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with Special Needs Statistical Analysis of Network Data with R *Mike Selby Elizabeth Castro Meghan Doherty Kishore Mahbubani Ayn Rand Matt Garrish Emilio Salgari Emily Neville O'Reilly TOC Team Kevin D Randle Julius Falconer William J. Conaway Sylvia Engdahl Pat Shaughnessy Yeliz Yesilada Yihui Xie Jeffrey Flesher Shane Peacock John Wilson Rick Novy Emilio Salgari Julius Falconer Julius Falconer Narasimha Karumanchi Beth R. Bernhardt Amir AghaKouchak R. Srinivasan Olav Martin Kvern Olav Martin Kvern Jason Matthews Steve Klabnik Mirela Roncevic Jeremy P. Jones Corey Sandler Lionel K Anderson MSc Mike Mayo Diane Burns Sushil C. Dimri Klaus Miesenberger Eric D. Kolaczyk*

freedom libraries the untold story of libraries for african americans in the south as the civil rights movement exploded across the united states the media of the time was able to show the rest of the world images of horrific racial violence and while some of the bravest people of the 20th century risked their lives for the right to simply order a cheeseburger ride a bus or use a clean water fountain there was another virtually unheard of struggle this one for the right to read although illegal racial segregation was strictly enforced in a number of american states and public libraries were not immune numerous libraries were desegregated on paper only there would be no cards given to african americans no books for them read and no furniture for them to use it was these exact conditions that helped create freedom libraries over eighty of these parallel libraries appeared in the deep south staffed by civil rights voter registration workers while the grassroots nature of the libraries meant they varied in size and quality all of them created the first encounter many african americans had with a library terror bombings and eventually murder would be visited on the freedom libraries with people giving up their lives so others could read a library book this book delves into how these libraries were the heart of the civil rights movement and the remarkable courage of the people who used them they would forever change libraries and librarianship even as they helped the greater movement change the society these libraries belonged to photographs of the libraries bring this little known part of american history to life

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on the one hand nobody wants to be a dick on the other hand dicks are everywhere they cut in line talk behind our backs recline into our seats and even have the power to morph into trolls online their powers are impressive but with a little foresight and thoughtfulness we can take a stand against dickishness today how not

to be a dick is packed with honest and straightforward advice but it also includes playful illustrations showing two well meaning but not always well behaved young people as they confront moments of potential dickishness in their everyday lives sometimes they falter sometimes they triumph but they always seek to find a better way and with their help you can too just see the agreement at the beginning of the book i pledge to use the tools and techniques provided in this book to help make the world a less dickish place doherty fires absurd twenty first century zingers that happen to be really really really funny starred booklist

this open access book consists of essays written by kishore mahbubani to explore the challenges and dilemmas faced by the west and asia in an increasingly interdependent world village and intensifying geopolitical competition the contents cover four parts part one the end of the era of western domination the major strategic error that the west is now making is to refuse to accept this reality the west needs to learn how to act strategically in a world where they are no longer the number 1 part two the return of asia from the years 1 to 1820 the largest economies in the world were asian after 1820 and the rise of the west however great asian civilizations like china and india were dominated and humiliated the twenty first century will see the return of asia to the center of the world stage part three the peaceful rise of china the shift in the balance of power to the east has been most pronounced in the rise of china while this rise has been peaceful many in the west have responded with considerable concern over the influence china will have on the world order part four globalization multilateralism and cooperation many of the world s pressing issues such as covid 19 and climate change are global issues and will require global cooperation to deal with in short human beings now live in a global village states must work with each other and we need a world order that enables and facilitates cooperation in our global village

anthem which was written during a break from the writing of the author s next major novel the fountainhead presents a vision of a dystopian future world in which totalitarian collectivism has triumphed to such an extent that even the word i has been forgotten and replaced with we the story takes place at an unspecified future date when mankind has entered another dark age technological advancement is now carefully planned and the concept of individuality has been eliminated a young man known as equality 7 2521 rebels by doing secret scientific research when his activity is discovered he flees into the wilderness with the girl he loves together they plan to establish a new society based on rediscovered individualism this is the revised version published in 1946 which went on to sell more than 3 5 million copies

ready to take your ebooks to the next level with epub 3 this concise guide includes best practices and advice to help you navigate the format s wide range of technologies and functionality epub 3 is set to turn electronic publishing on its head with rich multimedia reading experiences and scripted interactivity but this specification can be daunting to learn this book provides you with a solid foundation written by people involved in the development of this specification epub 3 best practices includes chapters that cover unique aspects of the epub publishing process such as technology content creation and distribution get a comprehensive survey of accessible production features learn new global language support features including right to left page progressions embed content with epub 3 s new multimedia elements make your content dynamic through scripting and interactive elements work with publication and distribution metadata create synchronized text and audio playback in reading systems learn techniques for fixed and adaptive layouts

metà del seicento inghilterra e francia combattono contro la potenza degli spagnoli e iniziano ad inviare navi corsare in scorribanda per l oceano per combattere quelle nemiche e danneggiare così il commercio delle loro colonie e nel1625 due navi con a bordo i primi corsari gettano l ancora davanti all isola di san cristoforo e vi si stabiliscono ma una nave spagnola distrugge dopo cinque anni la loro base e i pochi che riescono a sopravvivere trovano un rifugio all isola della tortuga facendone la base di partenza per tutte le loro spedizioni gli abitanti di santo domingo però vedendo che il loro commercio è in pericolo dopo un attacco riescono a sconfiggerli e ad allontanarli un giorno però i bucanieri e i filibustieri riescono a far ritorno all isola arriva intanto alla tortuga un nobile italiano circondato dal mistero un certo emilio signore di ventimiglia valpenta e roccabruna durante un assedio in europa durante la guerra fra francia e spagna gli spagnoli tagliata la ritirata comprano un duca fiammingo van guld ordinandogli di tradire i superstiti italo francesi rifugiatisi in una rocca riesce nel suo malvagio piano ma uccide il fratello maggiore di emilio che dopo essersi miracolosamente salvato dalla carneficina degli spagnoli per vendicarsi lo insegue nei caraibi dove lui e i suoi due fratelli diventano il corsaro nero rosso e verde nero il romanzo ha inizio quando due filibustieri carmaux e van stiller vengono ripescati dalla folgore nave filibustiera appartenente a emilio di roccabruna conte di valpenta e di ventimiglia conosciuto come il corsaro nero una volta a bordo i due raccontano al terribile comandante che suo fratello enrico di ventimiglia conosciuto come il corsaro rosso era stato impiccato nella piazza di maracaibo per ordine di van guld governatore della città emilio decide così di recarsi a maracaibo per sottrarre il cadavere del fratello e reclutati carmaux e van stiller affida il comando della nave a morgan suo luogotenente dopo aver catturato

una guardia spagnola e guadagnato l'aiuto di Moko un africano eremita i filibustieri giungono a Maracaibo dopo numerose avventure il corsaro riesce a rapire la salma del fratello e a imbarcarsi sulla Folgoredove dopo aver celebrato il funerale del fratello giura solennemente che sterminerà Van Guld e tutta la sua famiglia sulla strada del ritorno per la Tortuga i filibustieri assaltano una nave spagnola che trasporta una bionda fanciulla che si fa chiamare Honorata Willerman duchessa di Weltrendem di cui Emilio si innamora ricambiato dopo essersi imbattuti in un terribile uragano la nave giunge finalmente alla Tortuga qui il racconto si interrompe e l'autore introduce una parentesi storica citando le imprese di grandi filibustieri realmente esistiti e spiegando cosa siano la filibusteria e la bucaneria ha poi inizio il racconto della spedizione per assalire Maracaibo la caccia di Emilio lo porta insieme a Carmaux Wan Stiller Moko e il soldato che avevano catturato poco tempo prima promosso a guida del drappello nella foresta vergine lì il gruppo incontrerà coguari e puzze vampiri sabbie mobili e antropofagi giunti quasi alla meta il soldato e Moko si fermano mentre i tre filibustieri proseguono la caccia seguirà uno scontro contro le forze di Van Guld e l'assalto a Gibilterra finite queste avventure pericolose il corsaro scoprirà che Honorata è in realtà la figlia di Van Guld e combattuto tra onore e amore farà imbarcare la giovane su una scialuppa e l'abbandonerà in mare con enorme dolore il romanzo si conclude con Carmaux che dice al suo amico Wan Stiller guarda lassù il corsaro nero piange

dave has the usual adolescent problems mitigated by the consoling company of his cat recounted with humor and a realistic teenage voice this newbery award winner unfolds amid the excitement of 1960s new york city superb the new york times

2012 was quite a year for change in the publishing industry throughout the year we used the toc community site toc oreilly com to provide insightful analysis of the latest industry developments and since ours is a community site the articles we publish aren't just from the toc team we also feature perspectives from many of the top innovators and publishing experts it wasn't easy but we hand-picked the most noteworthy articles from 2012 for inclusion in this best of toc collection we think you'll agree that the more than 60 pieces featured here represent some of the most thought-provoking dialog from the past year we've arranged the articles by category so whether you're most interested in marketing revenue models production or innovation in general you'll find something to get your creative juices flowing

conspiracy theories run rampant in the world of the ufo and search for alien life some are government sanctioned some are government sponsored and more than

a few can be laid at the feet of ufo witnesses and ufo investigators untangle the truth from the theories thoroughly investigated by a former army officer and taken from his review of hundreds of historical and government documents and in person interviews alien mysteries conspiracies and cover ups chronicles more than 100 sightings events and discoveries of alien encounters government conspiracy and the influence of extraterrestrials on human events throughout history from prehistoric ufo sightings cave paintings and ancient astronauts to modern sightings around the world alien mysteries investigates claims of aliens living among us abductions of humans to alien spacecraft and accounts of interstellar cooperation since the ufo crash in roswell along with evidence of what the government knows and what it has covered up this discussion of the government secrets theories and mysteries surrounding aliens is packed with thought provoking stories and shocking revelations of alien involvement in the lives of earthlings a complete dossier on alien activities and government cover ups this revealing book includes a look at prehistoric ufo sighting indian cave paintings the peruvian dinosaurs the ica stones the majestic twelve the allende letters the faked photographs that have been published as the real thing the condon committee the roswell bodies the alien autopsy project moon dust the phoenix lights ancient astronauts the recent ufo crash in needles california and much more

it is the summer of 1728 and we are in the village of sherburn in the west riding of yorkshire with its handsome church boys grammar school ancient tavern and tranquil rural population below the church lies the site of the palace of the kings of elmete nearby across the common and past the woods are the grand houses of commissioner of the peace squire hawley at scarthingwell hall and magistrate sir ralph gascoigne at parlington hall an apparent conspiracy to re establish the sixth century ancient british kingdom of elmete has worrying and sometimes hilarious consequences for the hapless vicar whose meagre detective skills are stretched to their limit both the squire and sir ralph are only too happy to leave it all to the vicar until that is the vicar is arrested for gun smuggling and the squire disappears it then transpires however that the conspiracy is merely camouflage for a more interesting crime altogether this neat tale both faithfully recreates the atmosphere of an eighteenth century yorkshire village and offers the modern reader rare entertainment book reviews online publishedbestsellers website

a twenty four page booklet of the history of san miguel de allende from the settlement through the war for independence with historic pictures

here are the author s collected essays about her newbery honor book enchantress

from the stars and other young adult and adult science fiction novels plus two autobiographical essays her comments on enchantress deal with issues she would like all its readers to be aware of this is one of three books of essays that replace reflections on the future collected essays which has grown too long and covers too many topics most of the essays included appeared there so if you already have that book you don't need this one the other two replacement books including a number of new essays are focused on space and on the human mind

an under the hood look at how the ruby programming language runs code extensively illustrated with complete explanations and hands on experiments covers ruby 2 x

covering key areas of evaluation and methodology client side applications specialist and novel technologies along with initial appraisals of disabilities this important book provides comprehensive coverage of web accessibility written by leading experts in the field it provides an overview of existing research and also looks at future developments providing a much deeper insight than can be obtained through existing research libraries aggregations or search engines

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when adam s grandfather first suggests taking him on a quick trip to sweden to

celebrate his upcoming thirteenth birthday visions of being in one of the coolest places on earth and he's not thinking of the temperature dance in adam's mind but on his way there he reads that swedes have a darker past and present than he ever imagined then he finds himself alone and separated from his grandfather in busy stockholm he is followed by unsmiling strangers chased by ghosts down alleyways and constantly watched by the strangest girl he's ever seen and then another terror perhaps bigger than the terror of being lost begins to overwhelm him in this fast paced prequel to last message and double you the outwardly confident but often secretly anxious adam wanders the streets of stockholm

a trip to a remote lake in northern ontario with his grandfather doesn't thrill steve especially since his twin brother dj was taken to central america matters start to look up when his grandfather tells steve about the mysterious death of the artist tom thomson and sets him the task of finding thomson's missing skull steve loves mysteries but when odd things begin happening and strange people start threatening him steve wonders whether this is part of his grandfather's plan is this still a simple puzzle or is something far more sinister going on in this thrilling prequel to lost cause and broken arrow the history and mystery loving steve ends up in remote northern ontario

explains how to construct an epub file manually obsolete now that software is readily available but still interesting for the techie

due cacciatori di lontre della compagnia russo americana sandoe e mac doll vengono imbarcati su un sottomarino contro la loro volontà si ritrovano così a far parte dell'equipaggio del taimyr un geniale e futuristico battello subacqueo dalle possibilità infinite comandato dal misterioso ingegnere nikirka coadiuvato da un equipaggio di provata fedeltà la missione del taimyr è raggiungere il polo nord navigando esclusivamente sotto le acque pur con alcuni imprevisti e difficoltà la meta viene raggiunta il ritorno invece riserva delle conseguenze impreviste dopo la perdita del taimyr e dell'intero equipaggio il solo mac doll che dovrà lasciar morire l'amico sandoe sarà miracolosamente salvato da una nave di passaggio

struggling to maintain his usual round of pastoral care agricultural concerns family life and church services the vicar of sherburn in elmete 1686 1771 parson and part time farmer again finds himself embroiled in a murder investigation forced on him by the indolence of the local law officers he skitters about in pursuit of a one eared footpad a scarred man and an elusive pedlar is arrested and tried for theft thwarts a plot to murder the local miller and confronts a villainous highwayman all apparently

to no purpose however by resolutely excluding curses spirits and bogles the explanations offered by others and concentrating on rational solutions to the mystery he succeeds finally and triumphantly in identifying the murderer expertly edited for modern readers by the redoubtable mr falconer this second chronicle of the doings of the vicar of sherburn in elmete draws the reader cosily into eighteenth century village life where medicine is primitive travel arduous and time consuming and officers of the law less than eager to perform their functions book reviews online publishedbestsellers website

we are in the sleepy village of sherburn in elmete yorkshire in the year of grace 1729 when george bywater the vicar s servant is clubbed to death as he collects the parish tithes the vicar undertakes to track his killer unfortunately his efforts are thwarted at every turn threatened with violence arrested and tried on three separate occasions on charges that include murder harbouring a felon and poaching he is saved from transportation or worse only by an act of god naturally he is hauled before the archdeacon and then the archbishop himself for carrying out his investigation at the expense of his pastoral duties forbidden to proceed as he wishes he yet takes advantage of a tip off from a local magistrate and a chance encounter with a reformed footpad to pursue his inquiries in a pure spirit of duty of course and comes up with a peculiarly delicate challenge to his conscience this light hearted tale is the third chronicle from sherburn in which julius falconer presents for the modern reader the absurd adventures penned by the hapless vicar book reviews online publishedbestsellers website

coding interview questions is a book that presents interview questions in simple and straightforward manner with a clear cut explanation this book will provide an introduction to the basics it comes handy as an interview and exam guide for computer scientists programming puzzles for interviews campus preparation degree masters course preparation big job hunters apple microsoft google amazon yahoo flip kart adobe ibm labs citrix mentor graphics netapp oracle webaroo de shaw success factors face book mcafee and many more reference manual for working people topics covered programming basicsintroductionrecursion and backtrackinglinked lists stacks queues trees priority queue and heapsgraph algorithmssortingsearching selection algorithms medians symbol tableshashing string algorithms algorithms design techniques greedy algorithms divide and conquer algorithms dynamic programming complexity classes design interview questions operating system concepts computer networking basics database concepts brain teasers nontechnical help miscellaneous concepts note if you already have data structures and algorithms made easy no need to buy this

over one hundred presentations from the 35th annual charleston library conference held november 4 7 2015 are included in this annual proceedings volume major themes of the meeting included streaming video analysis and assessment demand driven acquisition the future of university presses and open access publishing while the charleston meeting remains a core one for acquisitions librarians in dialog with publishers and vendors the breadth of coverage of this volume reflects the fact that this conference is now one of the major venues for leaders in the publishing and library communities to shape strategy and prepare for the future almost 1 800 delegates attended the 2015 meeting ranging from the staff of small public library systems to the ceos of major corporations this fully indexed copyedited volume provides a rich source for the latest evidence based research and lessons from practice in a range of information science fields the contributors are leaders in the library publishing and vendor communities

this book provides a collection of the state of the art methodologies and approaches suggested for detecting extremes trend analysis accounting for nonstationarities and uncertainties associated with extreme value analysis in a changing climate this volume is designed so that it can be used as the primary reference on the available methodologies for analysis of climate extremes furthermore the book addresses current hydrometeorologic global data sets and their applications for global scale analysis of extremes while the main objective is to deliver recent theoretical concepts several case studies on extreme climate conditions are provided audience the book is suitable for teaching in graduate courses in the disciplines of civil and environmental engineering earth system science meteorology and atmospheric sciences

this book introduces platform firms as unique business models leveraging on the early literature on network economics and strategy frameworks this book explores how platform business firms evolve in the modern business world taking a strategic perspective this book engages the reader with core concepts case studies and frameworks for analyzing platform business firms this book differentiates platform business firms from traditional pipeline firms explores engagement with different actors value creation and operations of platforms elucidates resources and capabilities of platform firms that provide them sustained competitive advantage analyzes performance levers in operating platform business models including complementarities with other business models and discusses the sustainability of platform business models in the face of regulatory and societal challenges among others the book is designed as a primer for entrepreneurs setting up and operating platform business firms senior managers in large corporations repurposing their

resources to initiate network dynamics in their businesses early career managers and professionals engaging with myriad platform firms for their professional and personal needs this book intends to provide a decision maker with a portfolio of decisions to make to create operate sustain and generate value out of a platform business firm it is also useful for policy professionals to appreciate the economics and policy implications of regulating and governing platforms in a post digital world

sharpen your indesign skills with this definitive resource created specifically for design professionals who need to produce great work in indesign cc regardless of the delivery platform best selling authors olav martin kvern david blatner and bob bringhurst share their hands on techniques to help you master indesign s advanced layout tools this book is brimming with insightful advice illustrations and shortcuts that will have you producing high quality work in no time this is the book that experts open to find real answers to their questions about indesign it s written in a friendly visual style that offers accurate information and creative inspiration for every indesign user whether you re publishing to a tablet mobile phone or traditional print publication in real world adobe indesign cc you ll learn how to use the new creative cloud features and enhancements including managing font menu favorites qr codes and much more prep documents and use the improved epub export feature for web and mobile publishing take full advantage of the best typesetting features on the market use best practices for consistent color management increase productivity with scripts and other automation features

a guide to the desktop publishing and page layout program covers manipulation of text and graphics adding effects applying color and digital publishing

have you written a book and want advice on what to do next this manual teaches authors to convert and sell books as ebooks at no cost create blogs websites cover design convert formats upload to major retailers maximize search rankings sell with paypal buttons and more this book shows authors how to make market and sell ebooks all for free highly instructional a valuable read

the official book on the rust programming language written by the rust development team at the mozilla foundation fully updated for rust 2018 the rust programming language is the official book on rust an open source systems programming language that helps you write faster more reliable software rust offers control over low level details such as memory usage in combination with high level ergonomics eliminating the hassle traditionally associated with low level languages the authors of the rust programming language members of the rust core team share their

knowledge and experience to show you how to take full advantage of rust s features from installation to creating robust and scalable programs you ll begin with basics like creating functions choosing data types and binding variables and then move on to more advanced concepts such as ownership and borrowing lifetimes and traits using rust s memory safety guarantees to build fast safe programs testing error handling and effective refactoring generics smart pointers multithreading trait objects and advanced pattern matching using cargo rust s built in package manager to build test and document your code and manage dependencies how best to use rust s advanced compiler with compiler led programming techniques you ll find plenty of code examples throughout the book as well as three chapters dedicated to building complete projects to test your learning a number guessing game a rust implementation of a command line tool and a multithreaded server new to this edition an extended section on rust macros an expanded chapter on modules and appendixes on rust development tools and editions

e book vendors continue to experiment adjustments to business models consolidation of content and mergers with competitors mean constant change what s good for innovation can equal confusion when it comes to choosing an e book platform for your library making a sound purchasing decision requires research and close consideration of trade offs and roncevic s new issue of library technology reports will get you started based on surveys of e book vendors with an established presence in academic public and or k 12 library markets this report includes background and business model descriptions for 51 leading e book vendors four tables comparing content technical specifications functionality and business models an at a glance overview of platforms including vendor website urls bulleted checklists of factors to consider and questions to ask vendors an examination of the blurring channels of publisher aggregator and distributor platforms with advice to help you avoid content overlap

devonthink is an exceptional app for managing your documents and notes and is available for the mac iphone and ipad the book showcases how professional users leverage devonthink to stay productive in their work it aims to inspire you to tap devonthink to its full potential in this book you will learn how to organize large document sets in devonthink and tap into its superior search capabilities how to take notes in devonthink with automatic wiki linking to other notes how to use devonthink as a repository for sources through unique urls that provide a direct link to any source document for use in other apps like obsidian and tinderbox how to tap the ai built into devonthink to reveal relevant documents and notes automatically which is especially valuable in a database of thousands of documents how to use

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the fun is just a tap away with the nifty nook tablet it's an e reader it's a tablet and it's hot the nook tablet offers all the advantages of an android based tablet and this small trim book is packed with information about how to use it learn to set up your nook tablet navigate the touchscreen download and read e books access the internet use all the cool android apps that are included and much more find out how to create your own e books share books with others listen to music or watch streaming video on your nook tablet personalize your tablet add accessories and take advantage of all it offers explains the hybrid e reader tablet concept and shows how to navigate the nook tablet touchscreen connect wirelessly install software updates and use the built in web browser covers reading e books and how to adjust lighting and fonts for your reading comfort guides you through shopping for and downloading e books watching streaming video from netflix hulu and other sources and creating a slideshow of photos from your digital camera shows how to side load video and music from your computer listen to audiobooks and interact with nook tablet using the built in microphone tells how to personalize your nook tablet share e books and use all the built in android based apps just like the nook tablet itself nook tablet for dummies portable edition is packed with everything you need to be nooking in no time

save hours of worry this book has been written as a tutorial for authors wanting to publish ebooks using lulu's book publishing services it provides some simple to understand details on the structure of epubs and describes some of the tools used to create them the tutorial also shows how to validate epubs on your own pc before even attempting to upload them to lulu it also describes how to use the lulu epub publishing wizard and epub converter the guide includes many fault finding tips to deal with some of the lulu error messages and other common errors updated december 2013 with the latest important and helpful fault finding tips and information

this cinefile's guidebook covers the horror genre monstrously well find reviews of over 1 000 of the best weirdest wickedest wackiest and most entertaining scary movies from every age of horror atomic bombs mad serial killers zealous zombies maniacal monsters lurking around every corner and the unleashing of technology rapidly changing and dominating our lives slasher and splatter films italian giallo and japanese city stomping monster flicks psychological horrors spoofs and nature running amuck you will find these terrors and many more in the horror show guide

the ultimate frightfest of movies no gravestone is left unturned to bring you entertaining critiques fascinating top ten lists numerous photos and extensive credit information to satisfy even the most die hard fans written by a fan for fans the horror show guide helps lead even the uninitiated to unexpected treasures of unease and mayhem with lists of similar motifs including urban horrors nasty bugs mad scientists and maniacal medicos evil dolls bad hair days big bad werewolves most appetizing cannibals classic ghost stories fiendish families guilty pleasures literary adaptations horrible highways and byways post apocalyptic horrors most regrettable remakes towns with a secret and many more with reviews on many overlooked underappreciated gems new devotees and discriminating dark cinema enthusiasts alike will love this big beautiful end all be all guide to an always popular film genre with many photos illustrations and other graphics the horror show guide is richly illustrated its helpful appendix of movie credits bibliography and extensive index add to its usefulness

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algorithms are ubiquitous in the contemporary technological world and they ultimately consist of finite sequences of instructions used to accomplish tasks with necessary input values this book analyses the top performing algorithms in areas as

diverse as big data artificial intelligence optimization techniques and cloud cyber security systems in order to explore their power and limitations

the two volume set Incs 12376 and 12377 constitutes the refereed proceedings of the 17th international conference on computers helping people with special needs icchp 2020 held in lecco italy in september 2020 the conference was held virtually due to the covid 19 pandemic the 104 papers presented were carefully reviewed and selected from 206 submissions included also are 13 introductions the papers are organized in the following topical sections part i user centred design and user participation in inclusive r d artificial intelligence accessible and assistive technologies xr accessibility learning from the past addressing real user needs and the technical architecture for inclusive immersive environments serious and fun games large scale web accessibility observatories accessible and inclusive digital publishing at and accessibility for blind and low vision users art karshmer lectures in access to mathematics science and engineering tactile graphics and models for blind people and recognition of shapes by touch and environmental sensing technologies for visual impairment part ii accessibility of non verbal communication making spatial information accessible to people with disabilities cognitive disabilities and accessibility pushing the boundaries of inclusion using digital technologies and accessible elearning environments ict to support inclusive education universal learning design uld hearing systems and accessories for people with hearing loss mobile health and mobile rehabilitation for people with disabilities current state challenges and opportunities innovation and implementation in the area of independent mobility through digital technologies how to improve interaction with a text input system human movement analysis for the design and evaluation of interactive systems and assistive devices and service and care provision in assistive environments 10 chapters are available open access under a creative commons attribution 4 0 international license via link springer.com

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Uracil: Understanding and Addressing Common Challenges in Research and Application

Uracil, a pyrimidine base found in RNA, plays a crucial role in gene expression and various biological processes. While less commonly discussed than its DNA counterpart, thymine, uracil presents unique challenges and opportunities in research, diagnostics, and therapeutic development. Understanding its properties, reactions, and limitations is crucial for researchers and practitioners alike. This article addresses common questions and challenges associated with uracil, offering solutions and insights to facilitate effective work with this important molecule.

1. Uracil's Role and Significance: Beyond RNA

Uracil's primary function is as a component of RNA, where it pairs with adenine. Its presence in RNA, instead of thymine found in DNA, is a key distinguishing feature of these two nucleic acids. However, uracil's significance extends beyond its role in RNA transcription and translation. It is involved in:

- Regulation of gene expression:** Modified uracil derivatives, like pseudouridine, play crucial roles in RNA structure and function, influencing processes like mRNA splicing and stability.
- Deoxyribonucleic acid (DNA) repair:** Uracil can arise in DNA through deamination of cytosine. Its presence signals DNA damage, triggering repair mechanisms.
- Biosynthesis of pyrimidines:** Understanding uracil biosynthesis is critical in developing drugs targeting pyrimidine metabolism for cancer therapy.
- Analytical applications:** Uracil detection is used in various diagnostic tests, like monitoring the efficacy of cancer treatments targeting pyrimidine metabolism.

2. Challenges in Working with Uracil: Reactivity and Instability

Uracil's chemical properties pose several challenges: Deamination of Cytosine: Cytosine's spontaneous deamination to uracil is a major source of DNA mutations. This highlights the need for efficient DNA repair mechanisms. Reactivity with electrophiles: Uracil's nucleophilic nitrogens can react with electrophiles, modifying its properties and potentially hindering its function in biological systems. This must be considered when designing experiments involving uracil modification or synthesis. UV sensitivity: Uracil, like other pyrimidines, is susceptible to UV damage, leading to dimer formation and hindering its functionality. Appropriate precautions, such as working under low-light conditions and using UV-blocking containers, are essential. Solubility: Uracil's solubility can vary depending on the solvent and pH. Optimizing solubility is crucial for its use in experiments and applications.

3. Addressing Challenges: Practical Solutions and Strategies

Addressing the challenges involves carefully designed experimental protocols and strategic approaches: Preventing Deamination: Working under strictly controlled conditions, minimizing exposure to high temperatures and oxidizing agents, can help to limit spontaneous deamination. Protecting against Electrophilic Attack: Choosing appropriate reaction conditions and using protecting groups can prevent unwanted reactions with electrophiles. Minimizing UV Damage: Handling uracil under low-light conditions and using amber-colored glassware or containers can significantly minimize UV-induced damage. Solubility Enhancement: Utilizing appropriate solvents, such as DMSO or DMF, or preparing uracil solutions at higher temperatures can improve solubility. In some cases, the use of uracil derivatives with improved solubility can be considered.

4. Synthesis and Modification of Uracil

The synthesis of uracil and its derivatives is an active area of research with significant implications for drug discovery and materials science. Common methods include: Condensation reactions: These reactions involve combining appropriate

starting materials, often urea derivatives, to form the uracil ring system. Chemical modification: Existing uracil molecules can be modified to alter their properties, such as enhancing their solubility or reactivity. This involves targeted chemical reactions at specific positions on the uracil ring. Example: Synthesis of 5-fluorouracil, a common anticancer drug, involves fluorination of uracil at the 5-position. This modification alters the molecule's interactions with enzymes involved in pyrimidine metabolism, inhibiting cell growth.

5. Applications in Research and Diagnostics

Uracil's applications span various fields: RNA research: Uracil is crucial in studying RNA structure, function, and modification. Its presence in RNA helps elucidate various biological processes. Cancer diagnostics: Monitoring uracil levels or its metabolites in body fluids can provide insights into the effectiveness of cancer treatments. DNA repair studies: Studying uracil excision repair pathways can offer a better understanding of DNA damage and its repair. Drug development: Uracil analogs are used in designing drugs targeting various diseases, including cancer and viral infections.

Summary

Uracil, while less prominently featured than thymine, plays a crucial role in various biological processes. Its inherent reactivity and susceptibility to UV damage present challenges in handling and research. However, understanding these properties and employing suitable strategies, including controlled reaction conditions, protecting groups, and solubility enhancement techniques, allow for successful utilization in research and application. Its involvement in RNA function, DNA repair, and its use as a basis for various therapeutic agents underscore its continuing significance in biological and medicinal chemistry.

FAQs

1. What is the difference between uracil and thymine? Thymine contains a methyl group at the 5-position, which uracil lacks. This subtle difference influences their

properties and roles in DNA and RNA, respectively. 2. How is uracil detected in biological samples? Various techniques like HPLC, mass spectrometry, and spectroscopic methods can be employed for uracil detection and quantification in biological samples. 3. What are some common uracil analogs used in medicine? 5-fluorouracil (5-FU) is a well-known example used in cancer chemotherapy. Other analogs are under development for various therapeutic applications. 4. What are the environmental implications of uracil? While uracil itself is not considered a major environmental pollutant, the disposal of uracil-containing waste from research and pharmaceutical industries requires careful management. 5. How does uracil contribute to mutations? The spontaneous deamination of cytosine to uracil in DNA can lead to C-to-U transitions, which if not repaired, result in mutations.

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