

# Considerations and Future Directions for the Development of Open-Source, Public License, Pharmacometric Software

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Metrum Research Group



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# Free Software?

“**Free software** is a matter of liberty, not price. To understand the concept, you should think of **free** as in **free speech**, not as in **free beer**.”

- Richard M. Stallman

## Free Software, Free Society: Selected Essays of Richard M. Stallman



1983 - GNU (GNU's Not UNIX) project  
1989 - GPL (General Public License), copyleft

Introduction by Lawrence Lessig

Edited by Joshua Gay

GNU Press  
[www.gnupress.org](http://www.gnupress.org)  
Free Software Foundation  
Boston, MA USA

2002, Free Software Foundation, Inc.

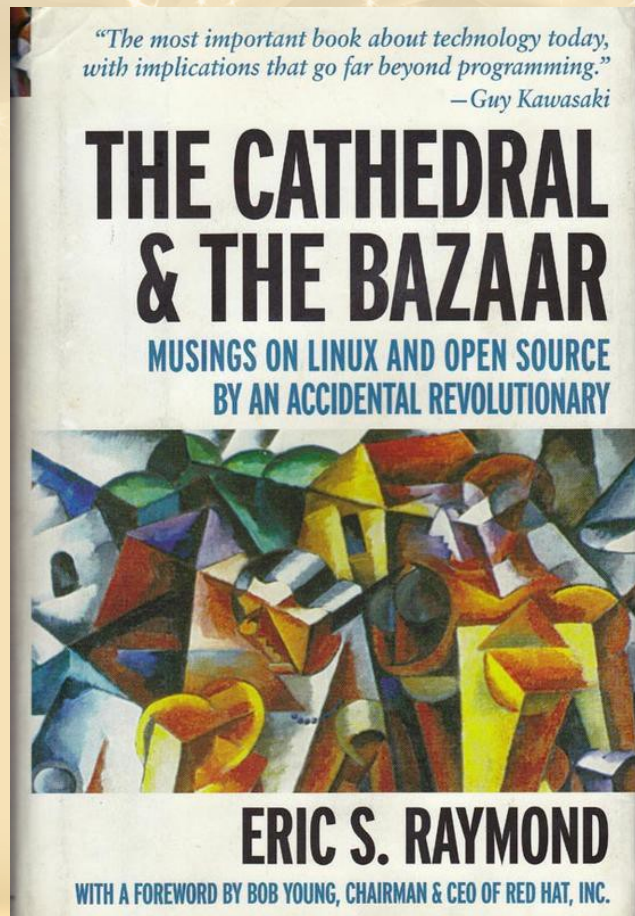


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# Linux



## The Cathedral

- Source code is available at each software release, but between-release code is restricted to an exclusive group of software developers (e.g. GNU Emacs and GCC).

## The Bazaar

- Source code is developed over the internet in view of the public. Linus Torvalds, leader of the Linux kernel project, considered the inventor of this process.



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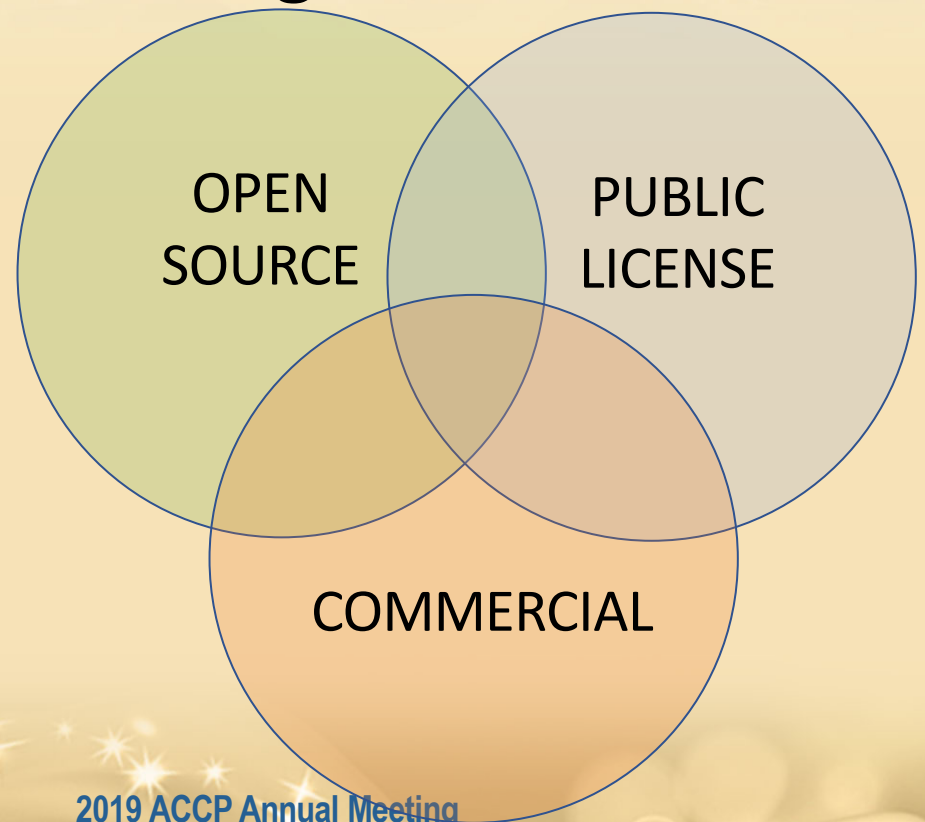
# Source Code AND Licensing Matter

Sometimes commercial software distributed as Open Source code

- Intellectual and practical value for end users
- Limited liberty, as stated by RMS

Open Source & Public License (OSPL)

- Extends the value across entire community and future tools
- Fosters liberty, creativity, growth



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# Factors Driving OSPL Software Development

- Community needs (features, urgency, direction) not met by commercial developers
- Commercial license limits freedom:  
“Freedom to use, study, distribute, and modify software” – RMS
- Full transparency and community involvement leads to more useful software
- OSPL fosters growth of science & technology



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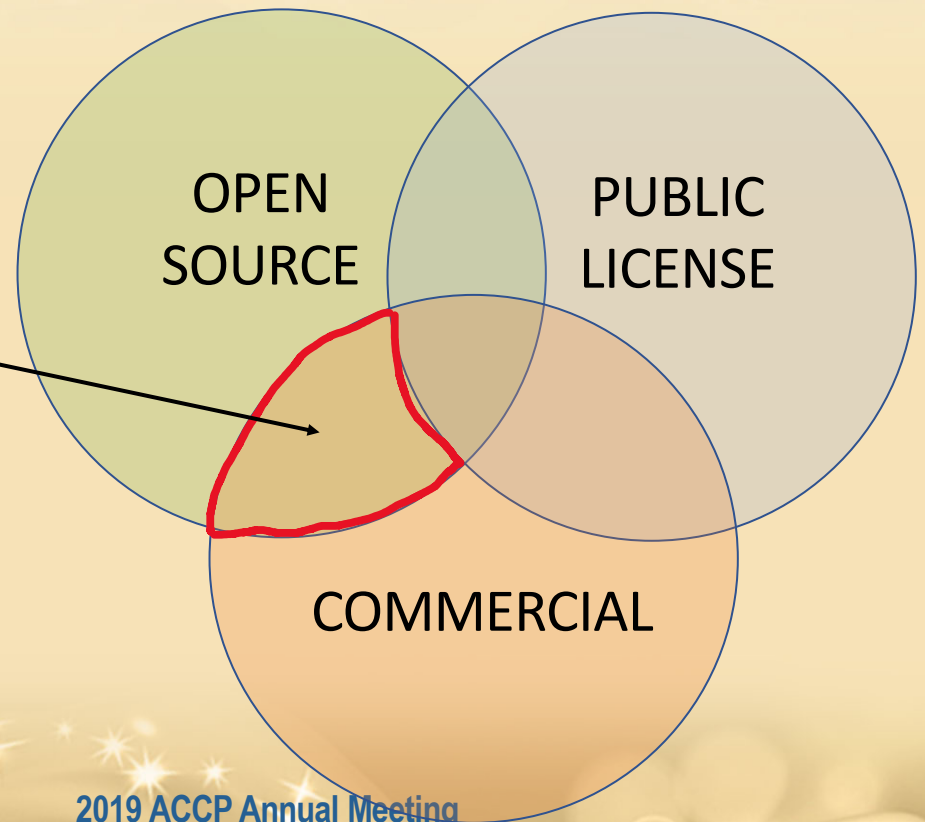


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# A Motivating Example: NONMEM® V 1.1.

- Commercial software, copyright UCSF, Distributed by GloboMax
- Open Source but not Public License



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*Fix data truncation bug (use WIDE option on \$DATA) and make source code changes:*

In C:\NMV\TR\:

Locate this line in READ3.FOR:

```
ELSEIF (VALUE(KK+J).GE.1000.0.AND.WIDE.NE.'Y') THEN
```

Replace with:

```
ELSEIF (VALUE(KK+J).GE.1000.0.AND.WIDE.NE.'Y'.AND.NSP.EQ.1)  
THEN
```

Locate and delete the following statement in READF.FOR:

```
IF (INOBS.GT.9999.AND.WIDE.EQ.'Y') CALL ERRMSG(283,' ',1)
```

<https://cognigencorp.com/nonmem/nm/99feb102004.html>



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*Bug with correlated epsilons across L2 records:*

*In C:\NMV\NM\OBJ2.FOR:*

*LOCATE the two lines of code:*

*IQ=0*

*IF (MODE.EQ.2) THEN*

*REPLACE these with:*

*IF (MODE.NE.3) THEN*

*IQ=0*

<https://cognigencorp.com/nonmem/nm/99feb102004.html>



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# An OSPL Solution

## **NMQual: A Tool to Automate Installation and Facilitate Qualification of NONMEM**

PAGE 2005 Meeting  
Pamplona, Spain  
June 16-17, 2005

Bill Knebel<sup>1</sup>, Tim Bergsma<sup>2</sup>, Leonid Gibiansky<sup>1</sup>, Jeffrey T. Hane<sup>1</sup>,  
Marc R. Gastonguay<sup>1</sup>

PAGE 14 (2005) Abstr 779 [[www.page-meeting.org/?abstract=779](http://www.page-meeting.org/?abstract=779)]  
<https://bitbucket.org/metrumrg/nmqual/wiki/Home>



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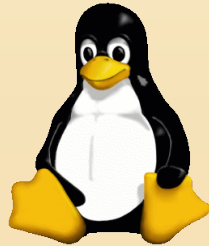
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# OSPL Software and Commercial Products

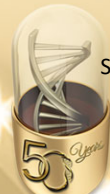


## Open Source & Public License Software

- Full functionality for all users

## Commercial Products Built Around OSPL

- Value-added solutions



Some images are registered trademarks of the companies identified.

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# Open Source Software Quality

- Professional Standards
  - SDLC
  - Quality documentation
- Full transparency to community (e.g. the Bazaar)

“Given enough eyeballs, all bugs are shallow.” - E.S. Raymond

“In the open-source software world, bug reports are welcome.”

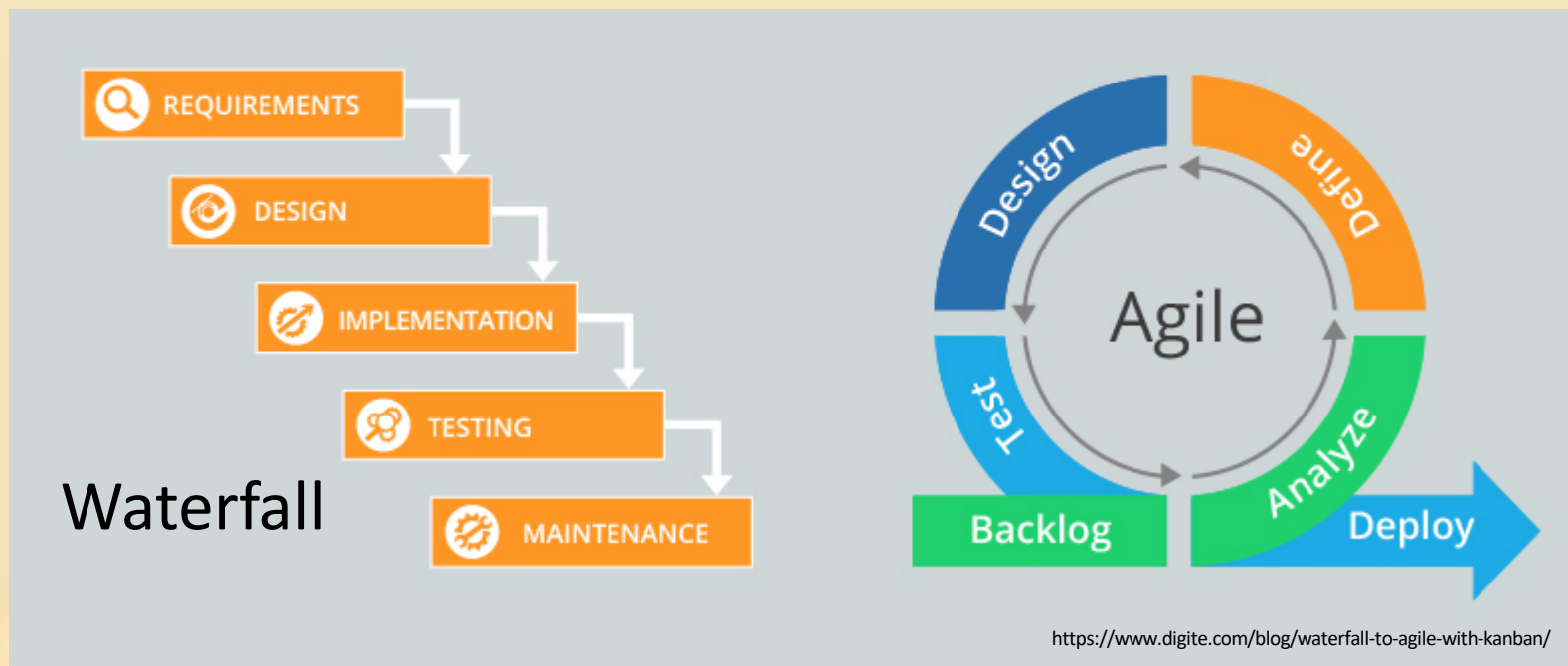
– A. Gelman



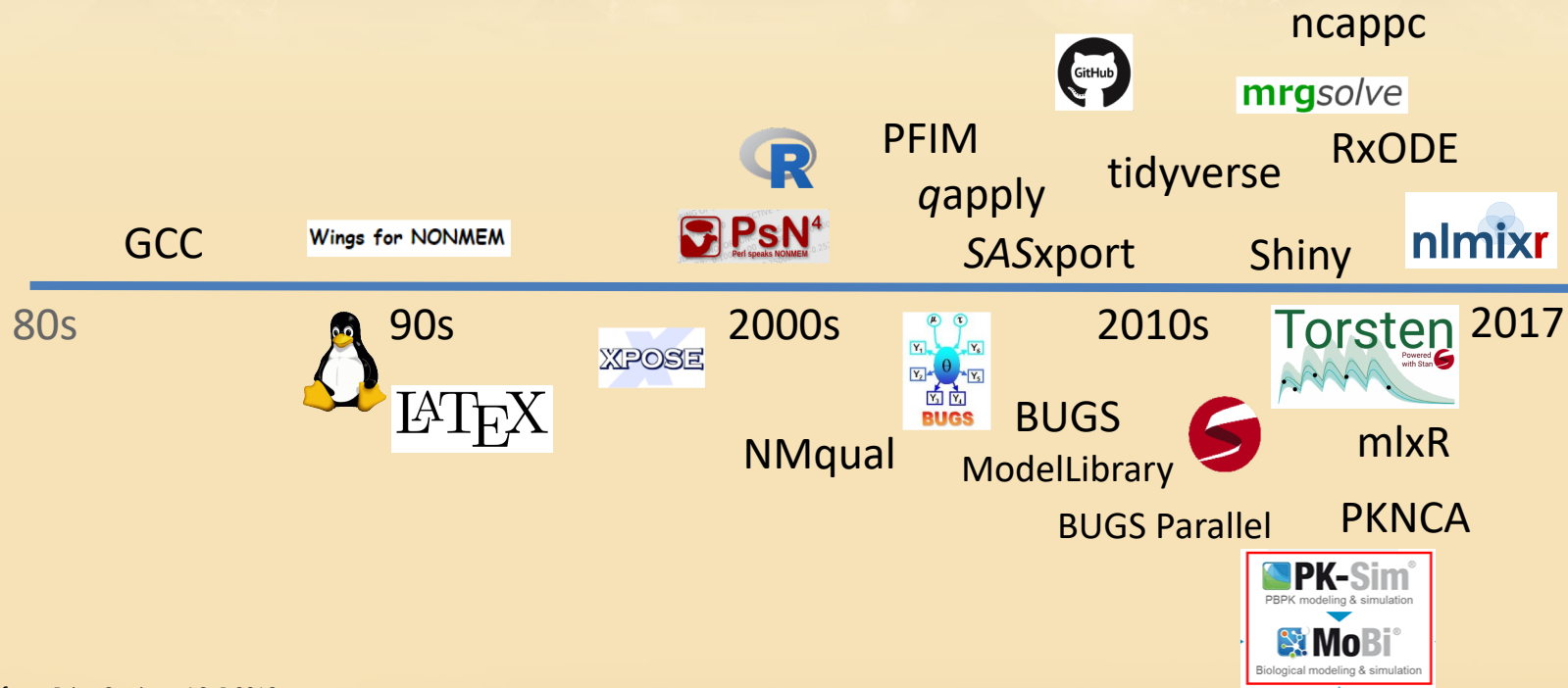
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# Software Development Life Cycle (SDLC)



# OSPL Software in Pharmacometrics



Adapted from: Brian Corrigan, ACoP 2016.

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# Which tools to select?

- Well-supported and well known language or platform
- Quality development practices
- Strong development team
- Strong community involvement
- Sustainable development project



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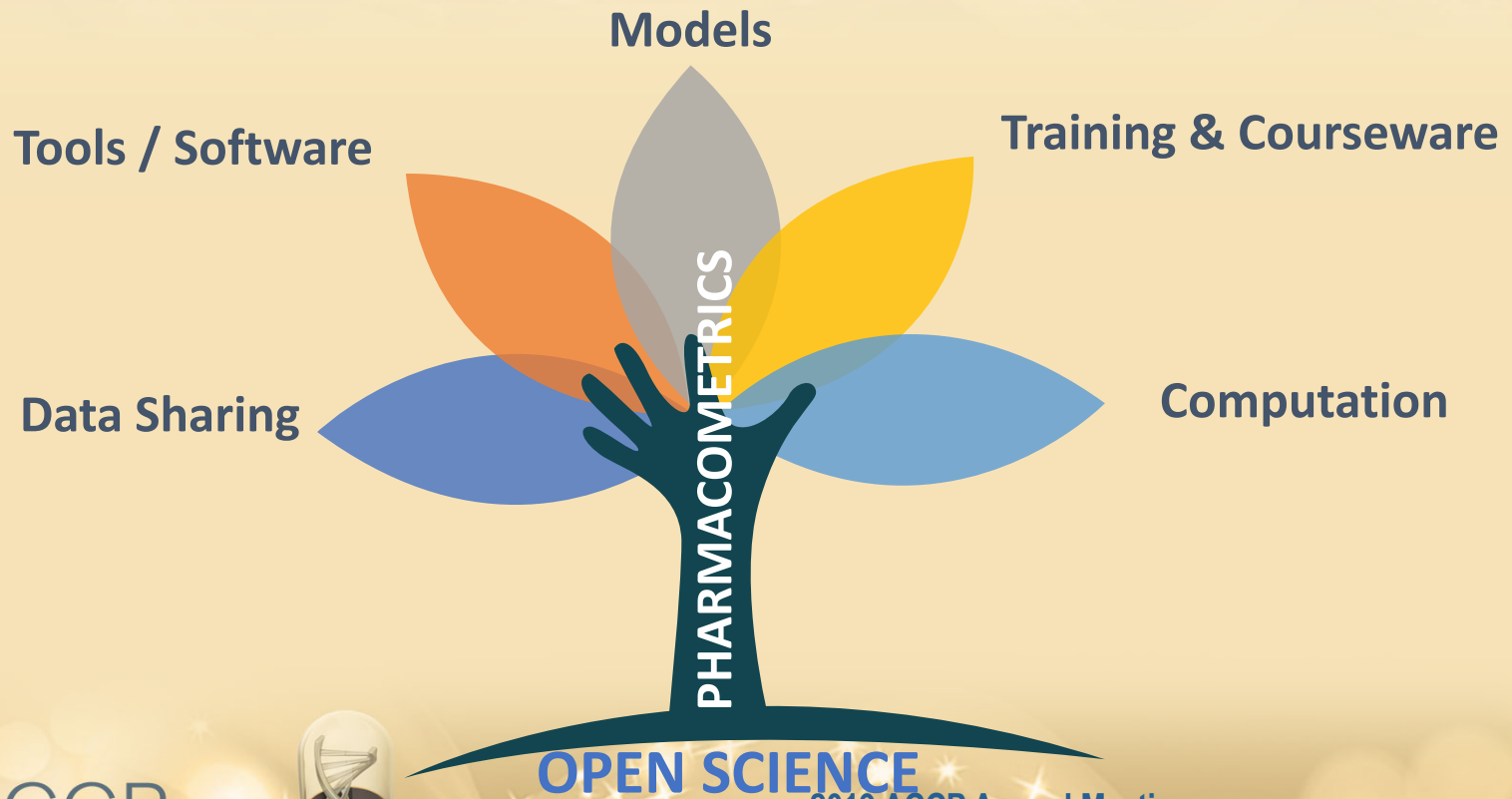
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# Growing the Science: A Community Responsibility



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# Training and Open Source Software

- Train scientists, not technicians of tools
- Independent, critical thinkers & resourceful problem solvers
- Competency with coding/scripting language
- OSPL Software is accessible
- Community support fosters shared learning
- Global interoperability
- Facilitates open science



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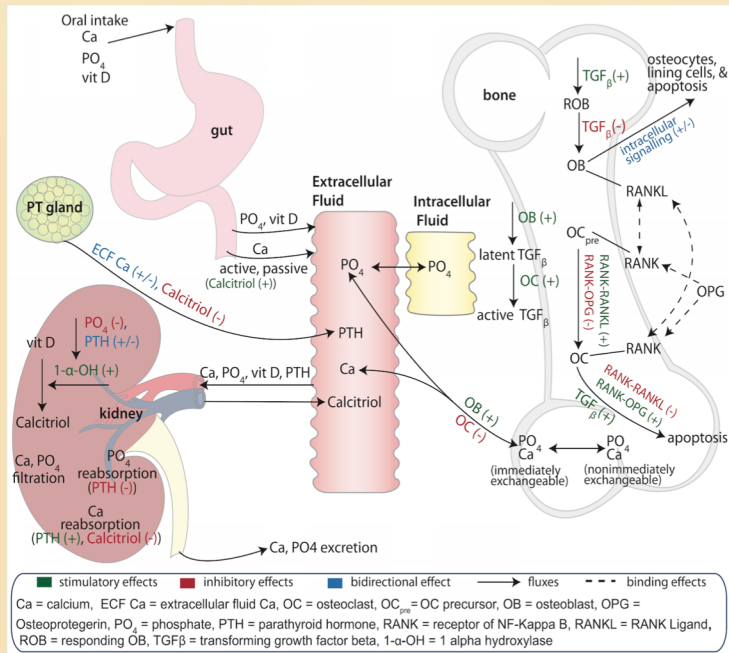
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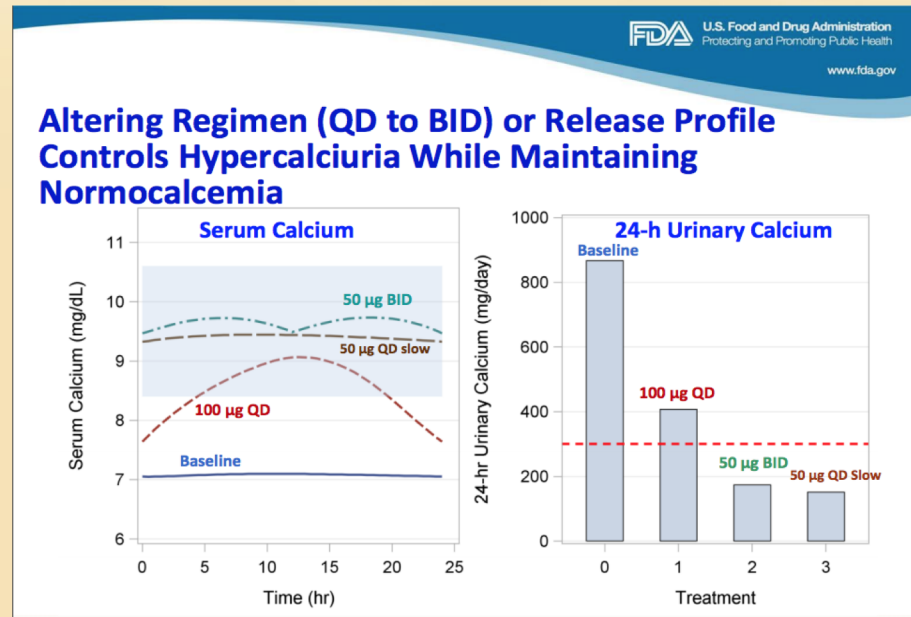
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# Utility of OSPL (*R, mrgsolve*) for Open Science

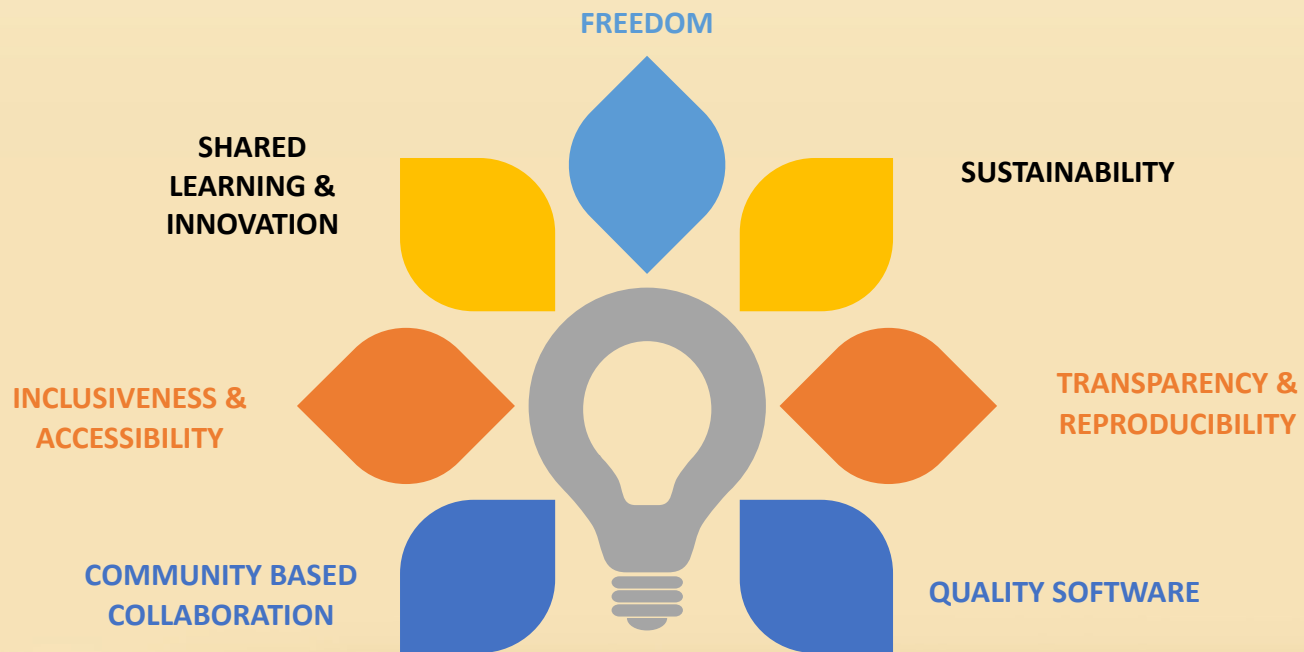


<https://github.com/metrumresearchgroup/OpenBoneMin>



<https://wayback.archive-it.org/7993/20170405215559/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM416168.pdf>

# Why Open Source Public License in Pharmacometrics?



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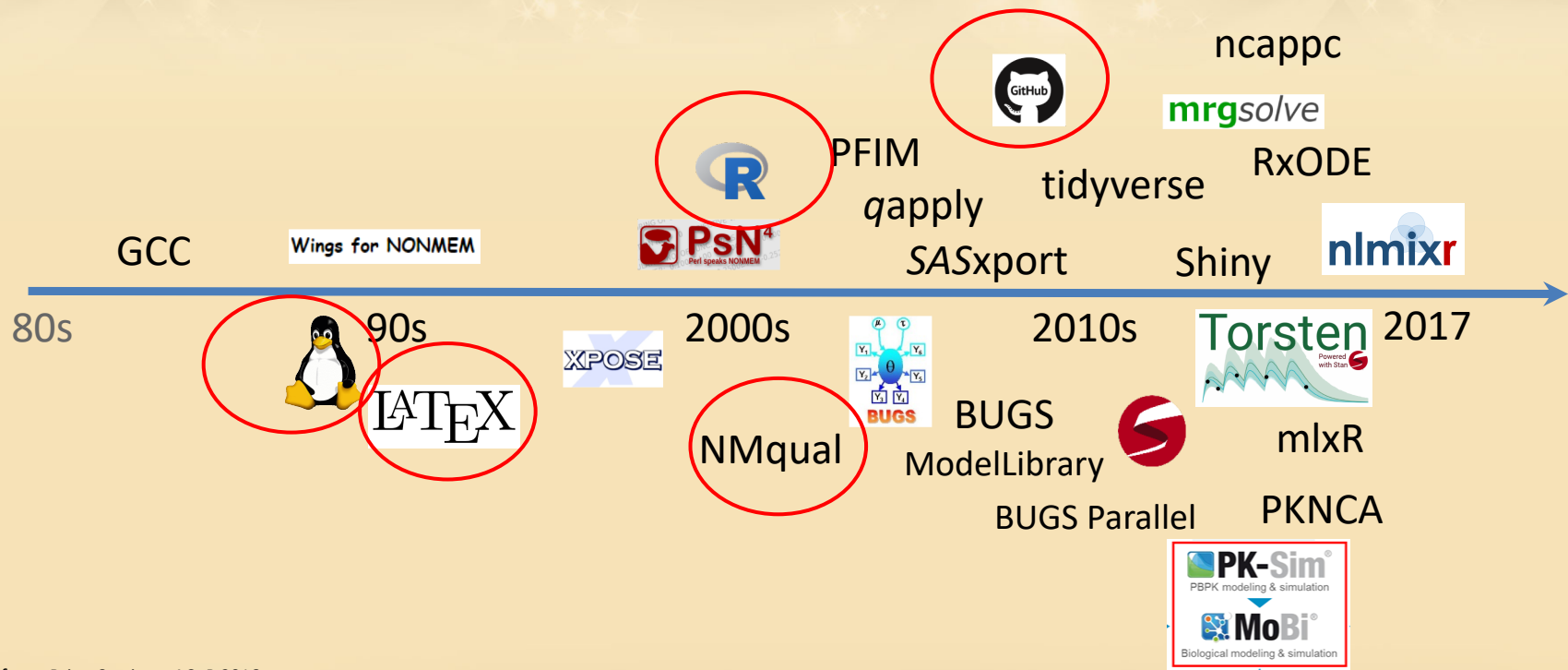
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# OSPL Software in Pharmacometrics: **Reproducible Research**

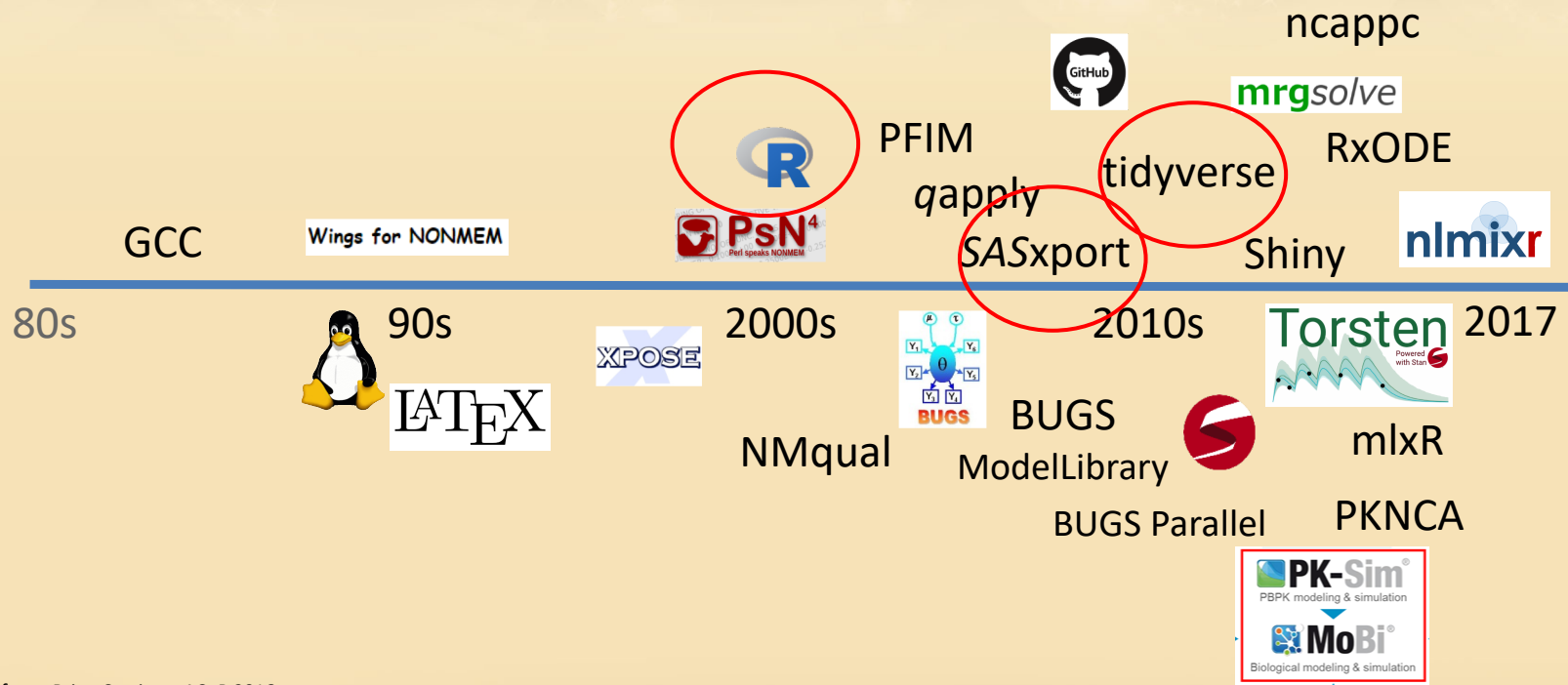


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# OSPL Software in Pharmacometrics: **Data Assembly**

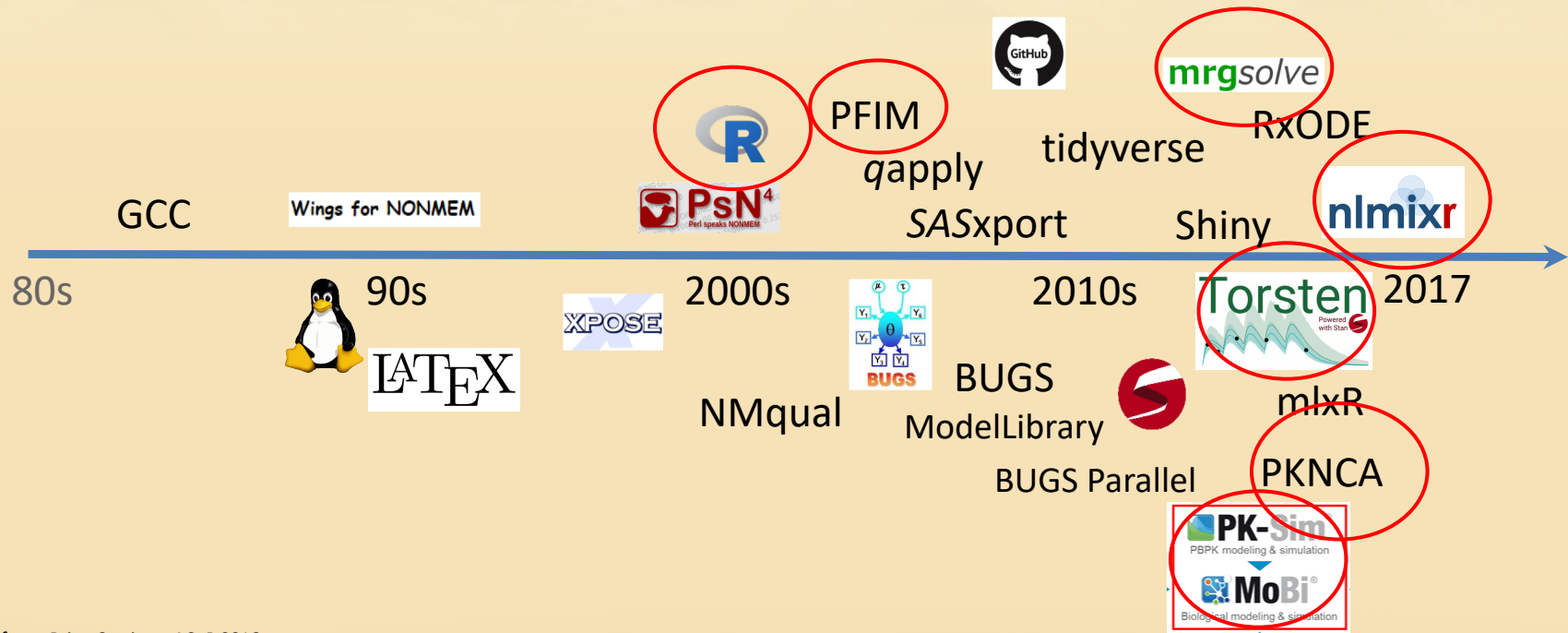


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# OSPL Software in Pharmacometrics: **Data Analysis**

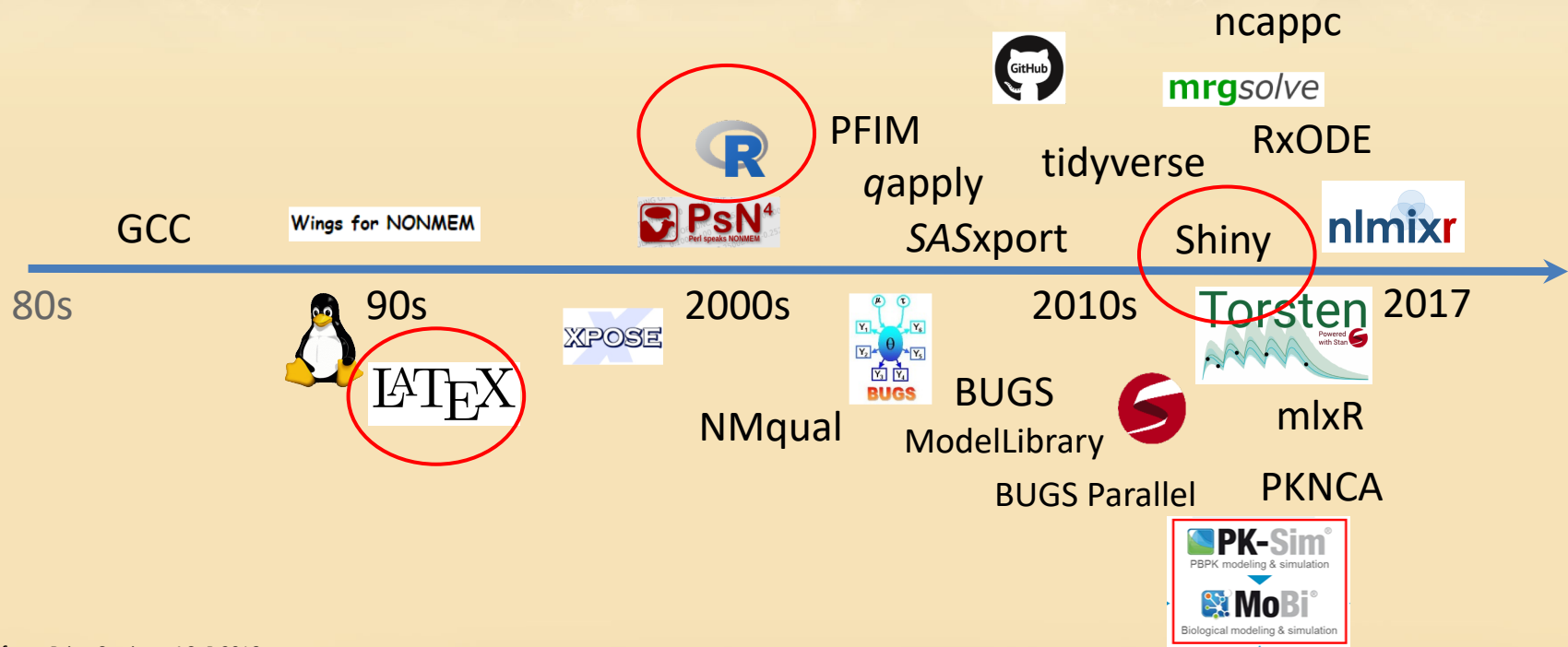


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# OSPL Software in Pharmacometrics: Results and Reporting



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Should the future of our science be constrained by the limited imagination and internal agendas of a few commercial software companies?



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# A Call to Action

Support open-source, public license software projects...

- in-kind effort
- use & feedback
- funding



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