Availability of Model Code from Published Computational Physiology Models

Graham Kim, John Gennari
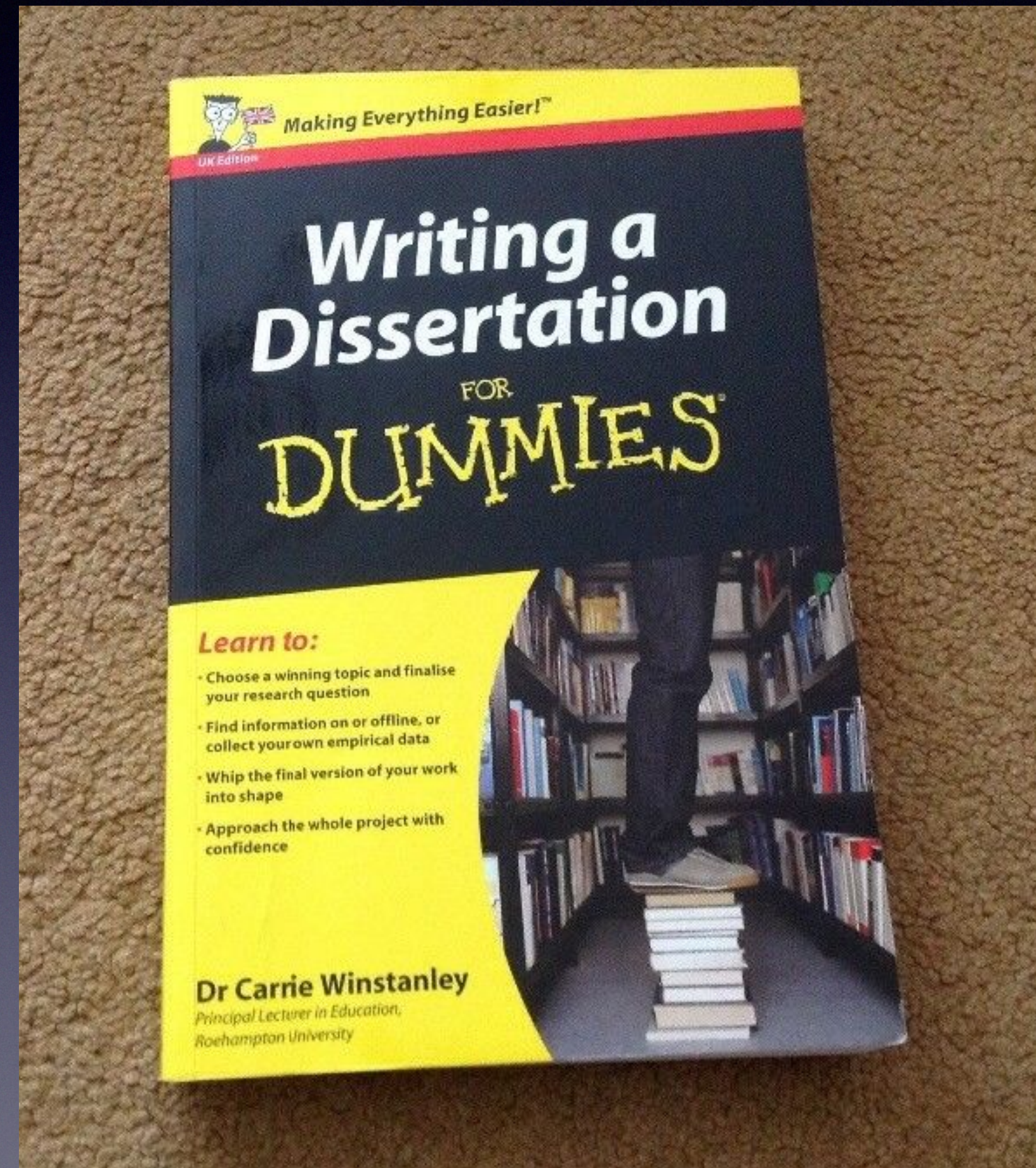
Biomedical and Health Informatics
University of Washington

Clinical Data + Models

- Abundance of existing clinical data

- Existing computational physiology models
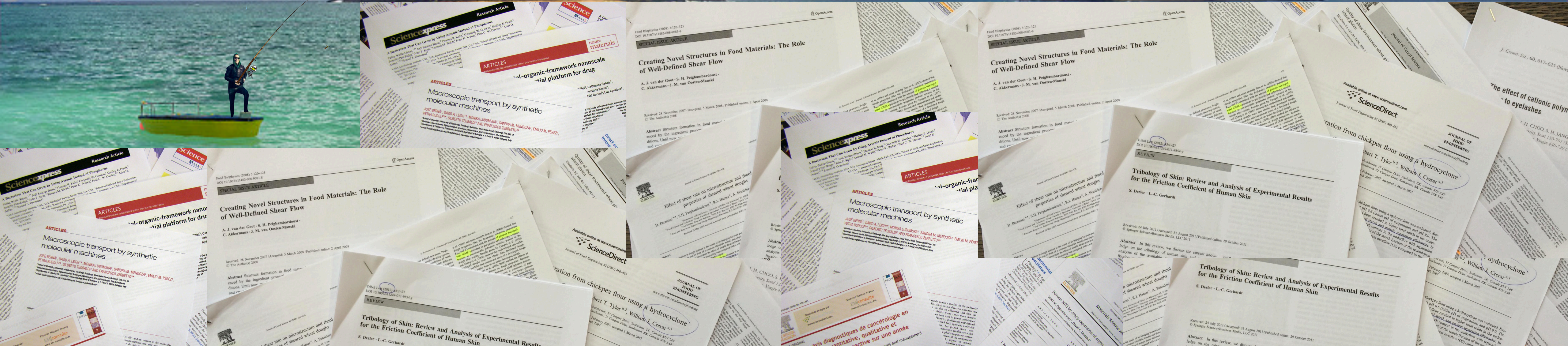
- Using clinical data for patient-specific modeling

Curated Model Repositories

- BioModels Database

- Physiome Model Repository

- **But what about model publications in the literature?**

What percentage of model publications make model code available?

Modelling the Response of FOXO Transcription Factors to Multiple Post-Translational Modifications Made by Agei...

Graham R. Smith, Daryl P. Shanley

Supporting Information

Dataset_S3.xml

```xml
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level2/version3" level="2" version="
    <model id="Foxo_PTMs" name="Foxo_PTMs">
        <listOfUnitDefinitions>
            <unitDefinition id="volume">
                <listOfUnits>
                    <unit kind="litre" scale="-3"/>
                </listOfUnits>
            </unitDefinition>
            <unitDefinition id="substance">
                <listOfUnits>
                    <unit kind="item"/>
                </listOfUnits>
            </unitDefinition>
            <unitDefinition id="time">
                <listOfUnits>
                    <unit kind="second" multiplier="60"/>
                </listOfUnits>
            </unitDefinition>
        </listOfUnitDefinitions>
        <listOfCompartments>
            <compartment id="extracellular" size="8.3e-12"/>
            <compartment id="cellsurface" size="6.4e-14" outside="extracellular".
            <compartment id="cytoplasm" size="1.65e-11" outside="cellsurface"/>
            <compartment id="nucleus" size="5e-13" outside="cytoplasm"/>
            <compartment id="dnabound" size="1e-13" outside="nucleus"/>
        </listOfCompartments>
        <listOfSpecies>
            <species id="null" compartment="cytoplasm" initialAmount="0" hasOnly
            <species id="degr_Foxo1" compartment="cytoplasm" initialAmount="0" h
            <species id="cytoplasm_Foxo1_Pa0_pUb0" compartment="cytoplasm" initi
```

download

Search

- PubMed

- MeSH terms - "Models, Biological"[MH] AND "Computer Simulation"[MH] AND Humans[Mesh]

- Articles published up to May 11, 2018

- Excluded review articles and meta-analysis

Results

- Total models retrieved: 6,909

- Excluded:

  - Non-computational models (e.g., simple mannequin)

  - Studies using previously published models

  - Statistical models without biological mechanism

  - Image/signal processing models
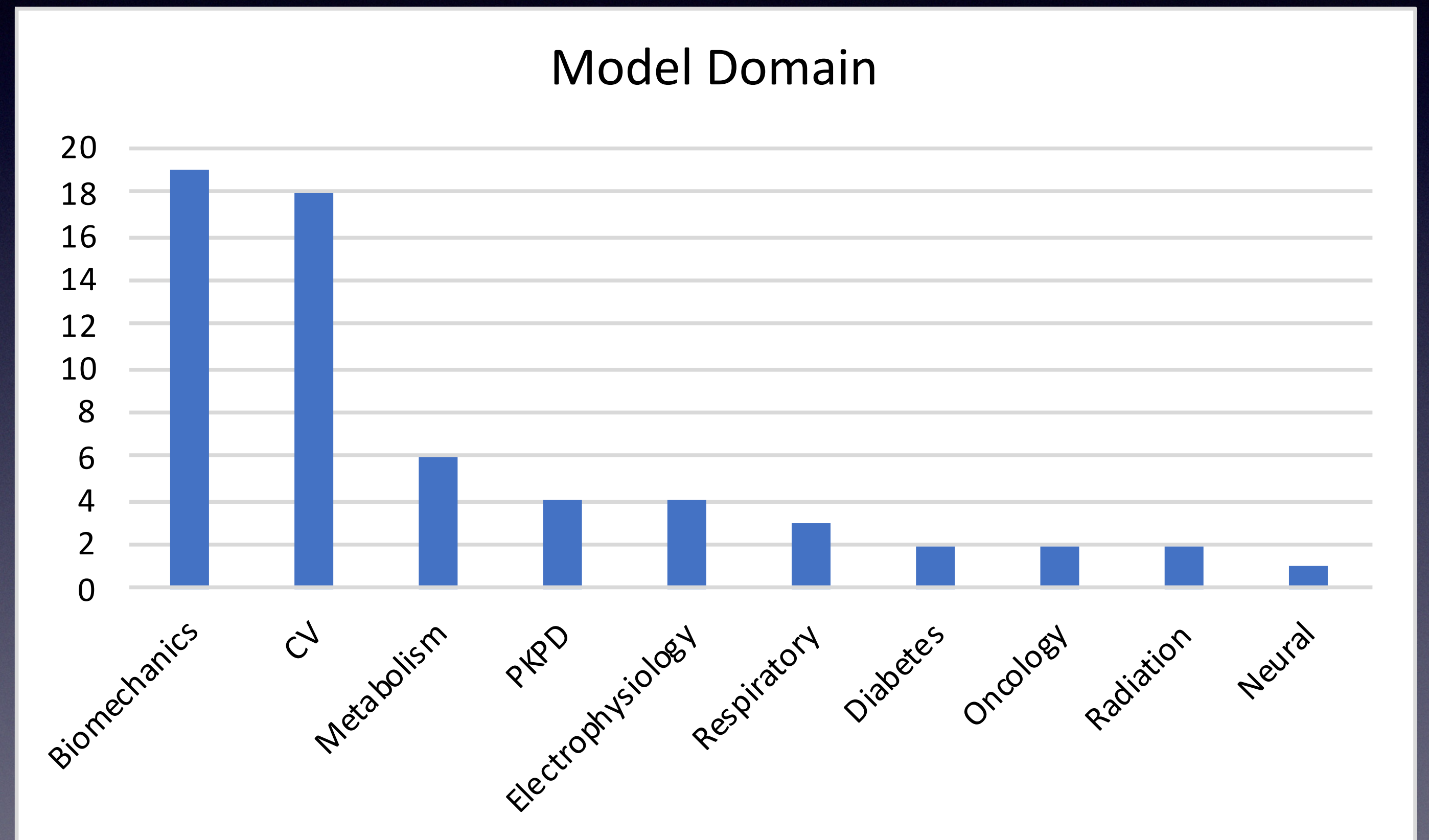
Results

- Sampled for analysis: 50

  - Biological domain

  - Modeling paradigm

  - Modeling language
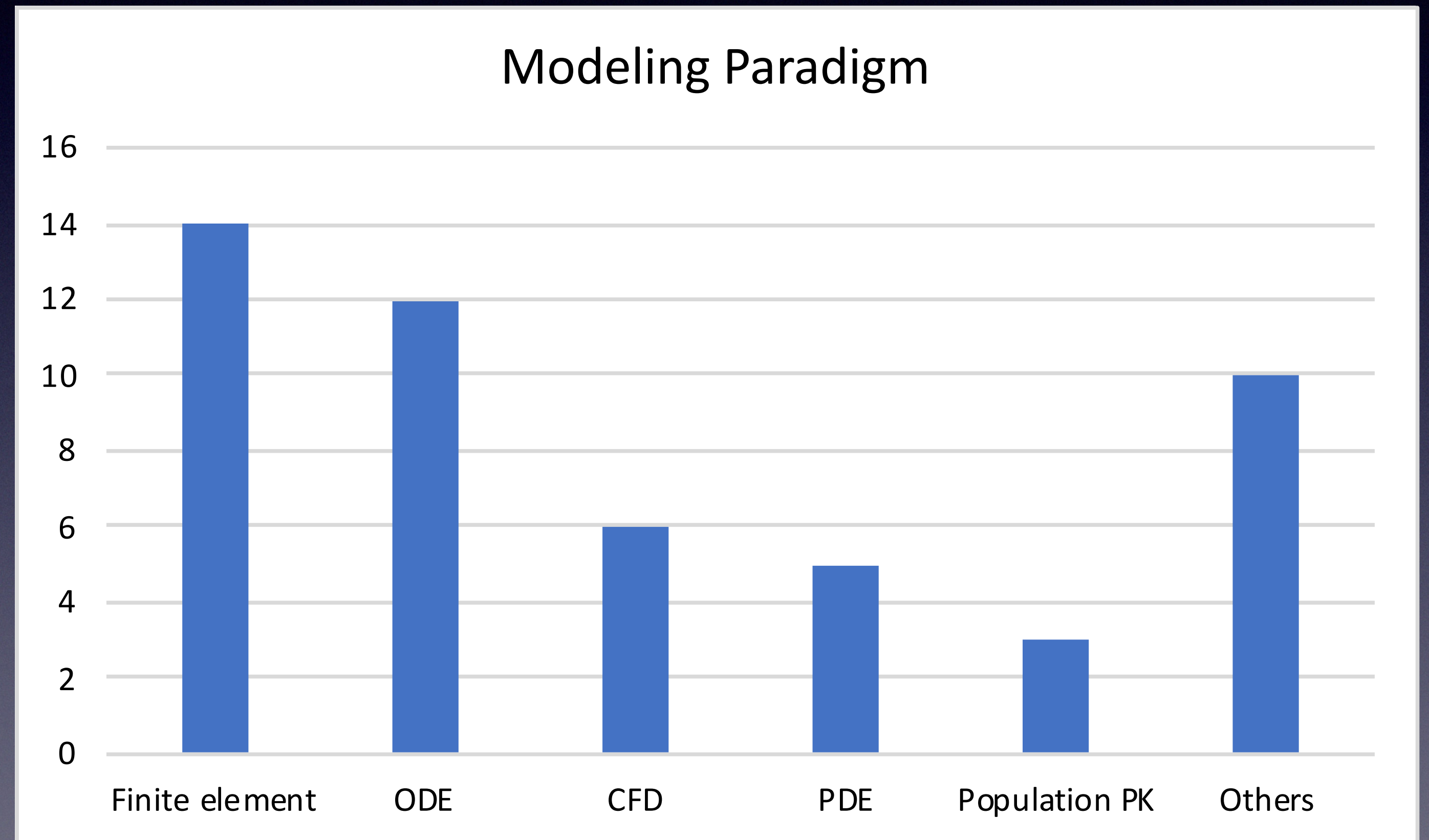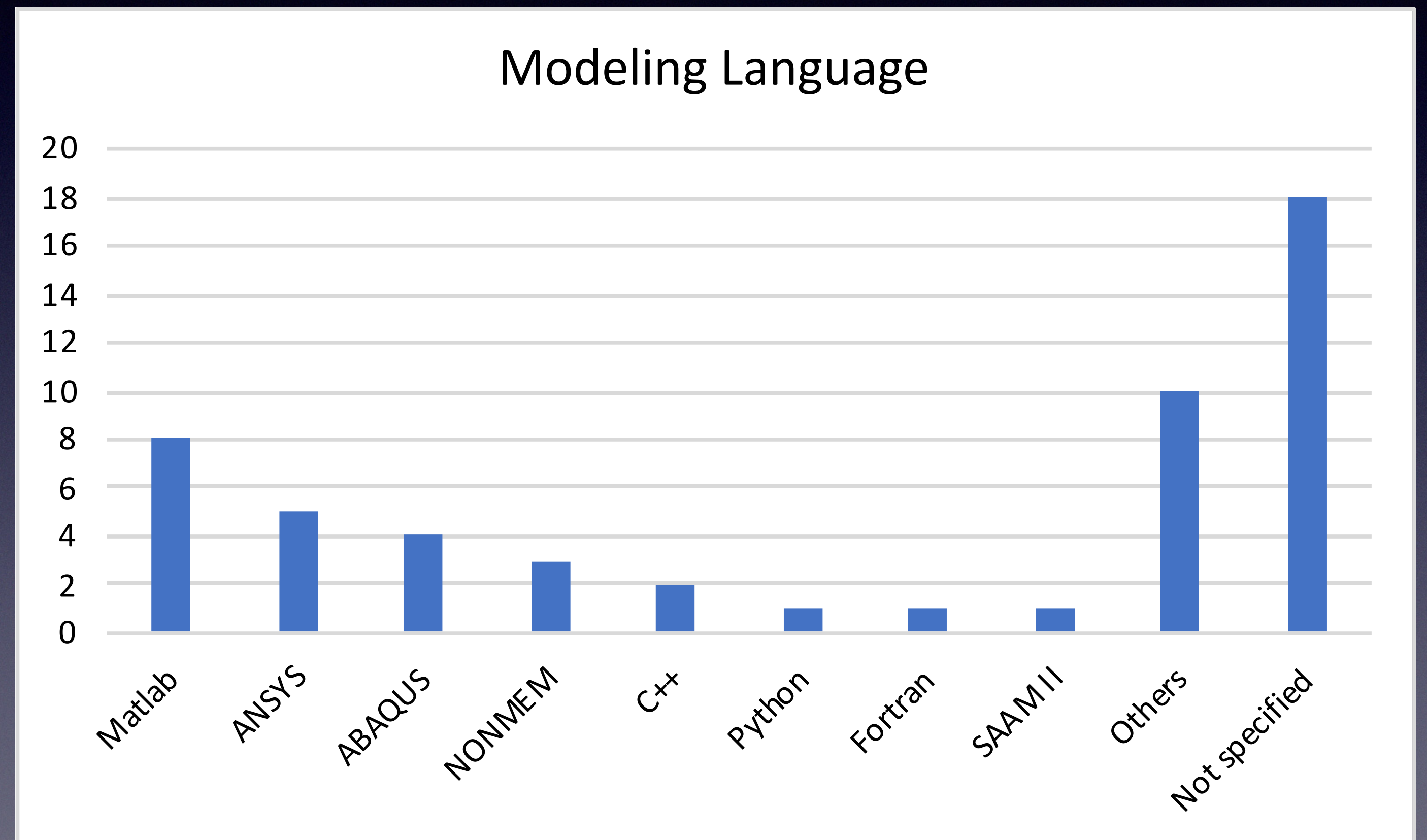
  - Model code availability

Results

- Sampled for analysis: 50

- **Biological domain**

- Modeling paradigm

- Modeling language

- Model code availability

Model Domain

Results

- Sampled for analysis: 50

  - Biological domain

  - **Modeling paradigm**

  - Modeling language

  - Model code availability

Modeling Paradigm

Results

- Sampled for analysis: 50

  - Biological domain

  - Modeling paradigm

  - **Modeling language**

  - Model code availability

Modeling Language

Results

- Sampled for analysis: 50

  - Biological domain

  - Modeling paradigm
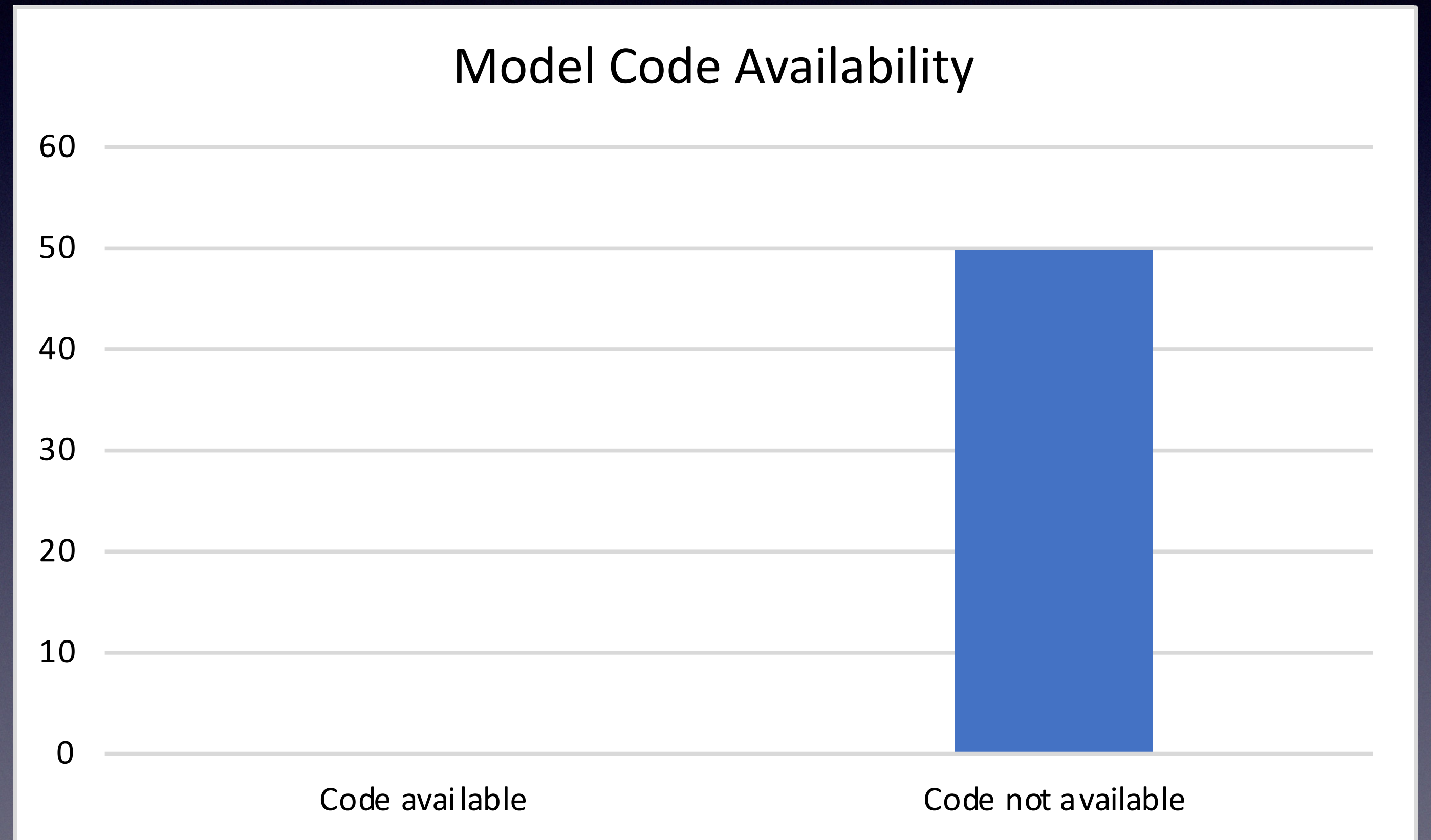
  - Modeling language

  - **Model code availability**

Model Code Availability

60	
50	
40	
30	
20	
10	
0	
Code available	Code not available

Search - Cardiovascular

- PubMed

- MeSH terms - "**Models, Cardiovascular**"[MH] AND "Computer Simulation"[MH] AND Humans[Mesh]

- Articles published up to May 4, 2018

- Excluded review articles and meta-analysis

Results - Cardiovascular

- Total models retrieved: 1,111

- Excluded:

  - Non-computational models

  - Studies using previously published models

  - Statistical models without biological mechanism
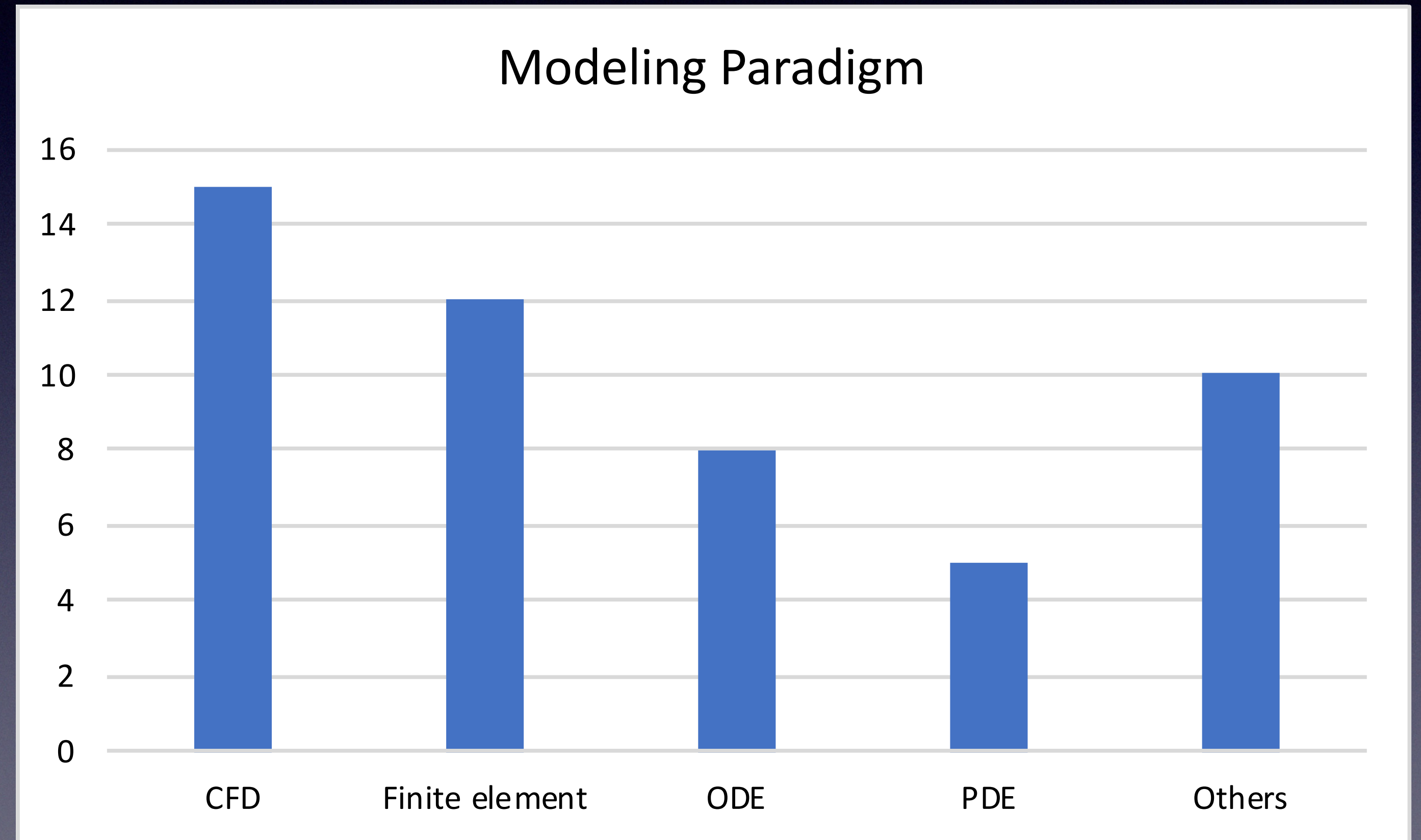
  - Image/signal processing models

Results - Cardiovascular

- Sampled for analysis: 50

  - Modeling paradigm

  - Modeling language
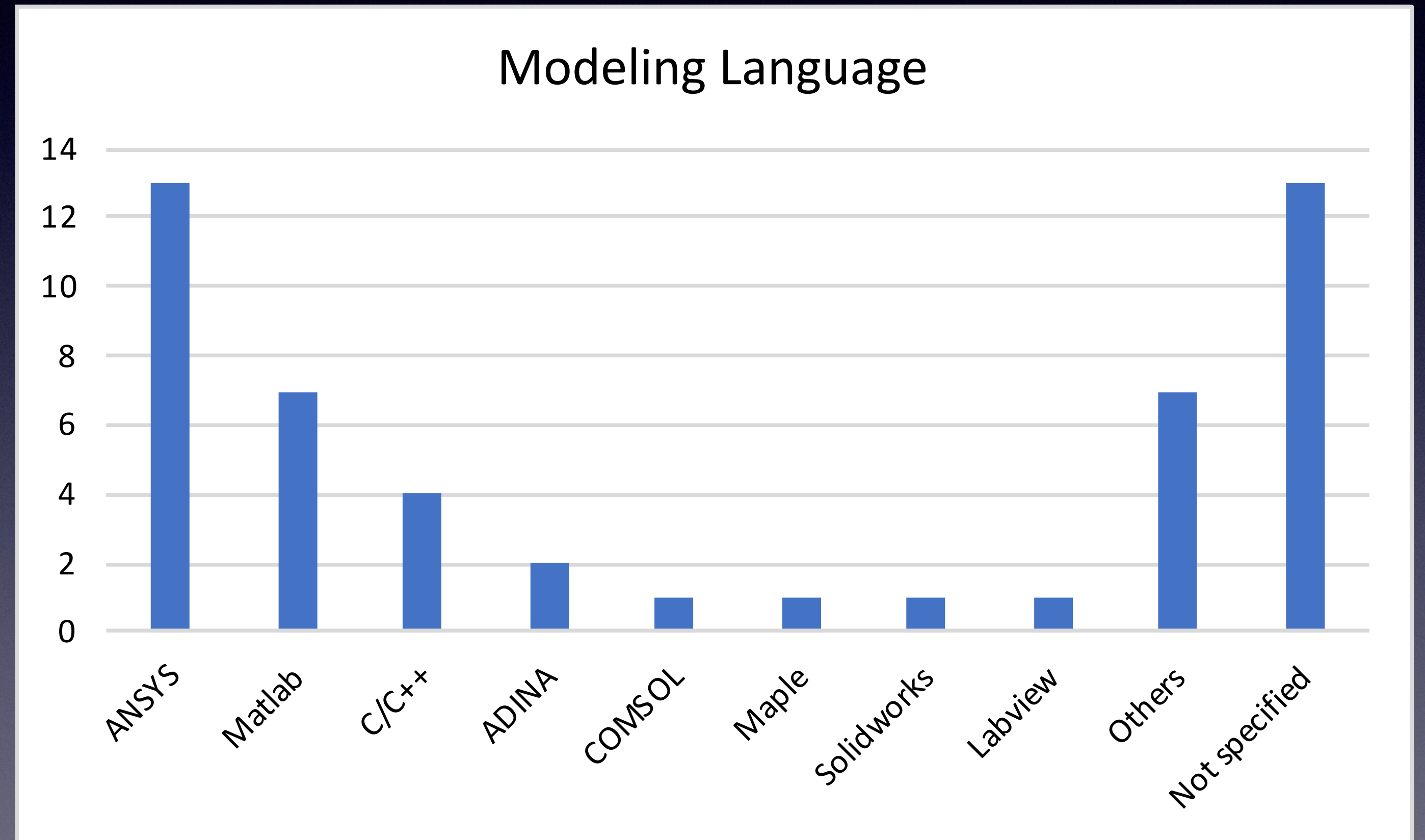
  - Model code availability

Results - Cardiovascular

- Sampled for analysis: 50

  - **Modeling paradigm**

  - Modeling language

  - Model code availability

Modeling Paradigm

Results - Cardiovascular

- Sampled for analysis: 50

  - Modeling paradigm

  - **Modeling language**

  - Model code availability

Modeling Language

Results - Cardiovascular

- Sampled for analysis: 50

  - Modeling paradigm

  - Modeling language

  - **Model code availability**

Model Code Availability

Search - Diabetes

- *The impact of mathematical modeling on the understanding of diabetes and related complications* by Ajmera, et al. 2013

- ~200 total models reviewed in this paper

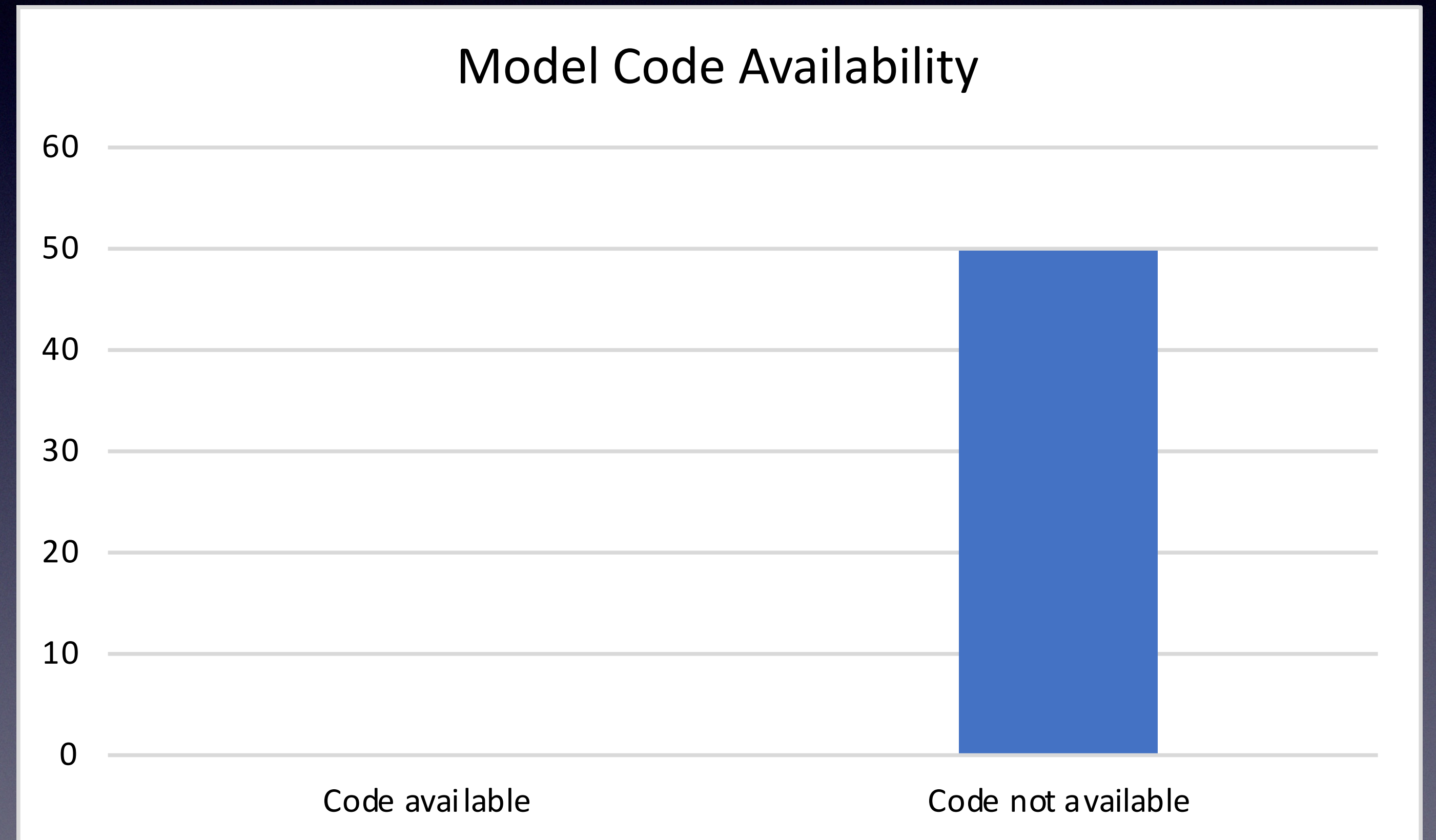- 96 model publications listed as "Clinical Models"

Results - Diabetes

- Sampled for analysis: 50

  - Modeling paradigm

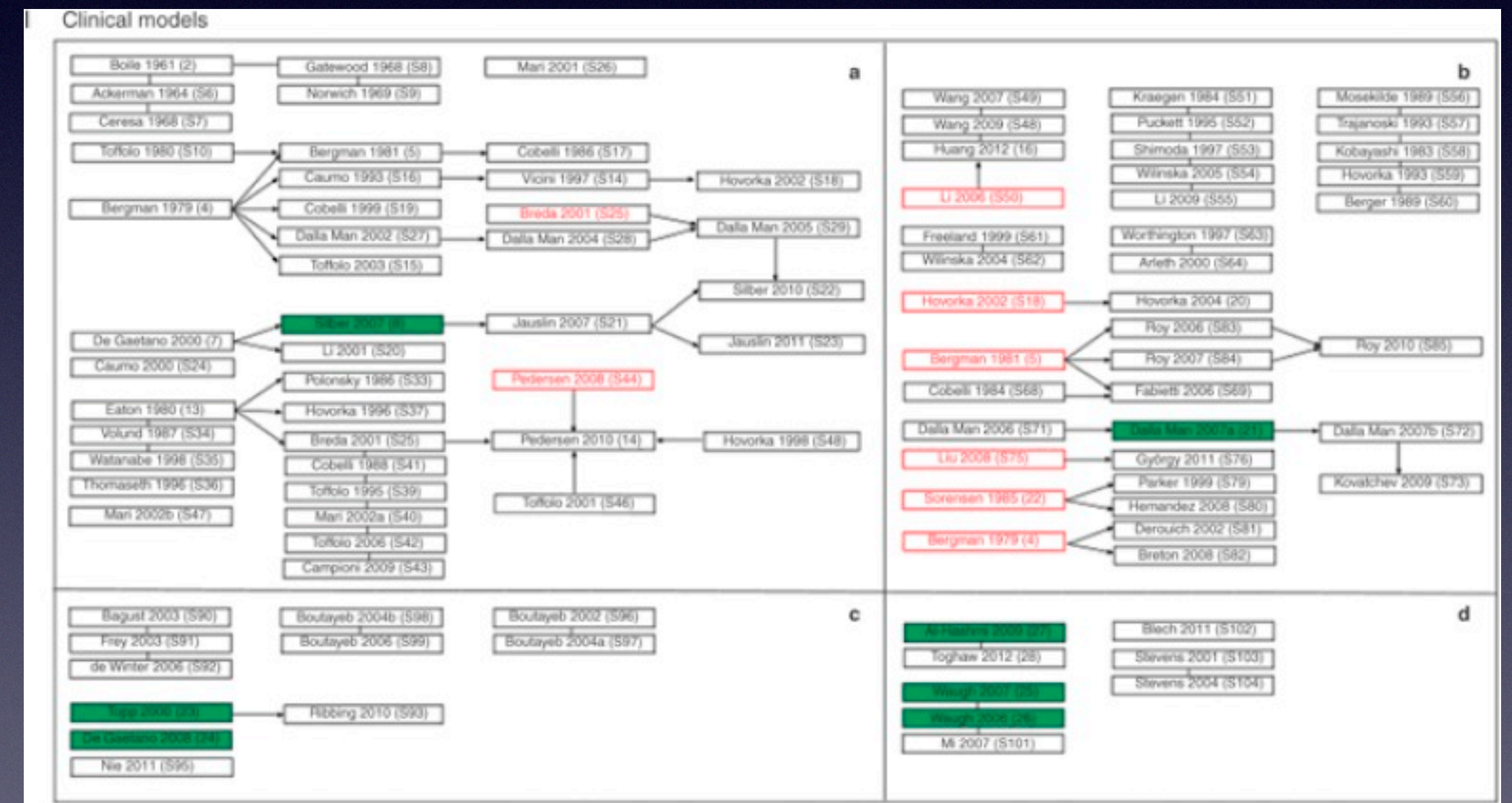 - Modeling language

  - Model code availability

Results - Diabetes

- Sampled for analysis: 50

  - **Modeling paradigm**

  - Modeling language

  - Model code availability

Modeling Paradigm

Results - Diabetes

- Sampled for analysis: 50

  - Modeling paradigm

  - **Modeling language**
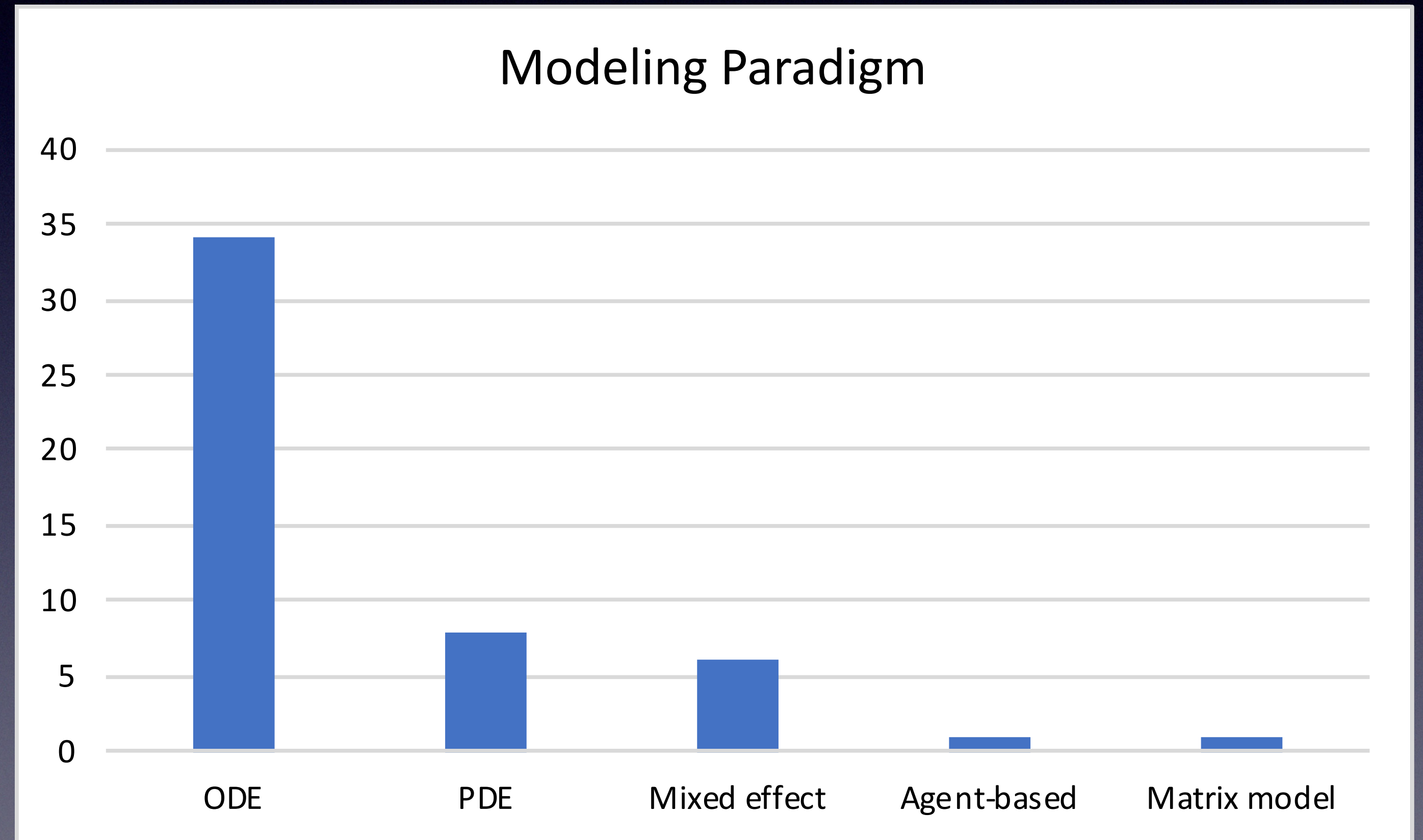
  - Model code availability

Modeling Language

Results - Diabetes

- Sampled for analysis: 50

  - Modeling paradigm

  - Modeling language

  - **Model code availability**

Model Code Availability
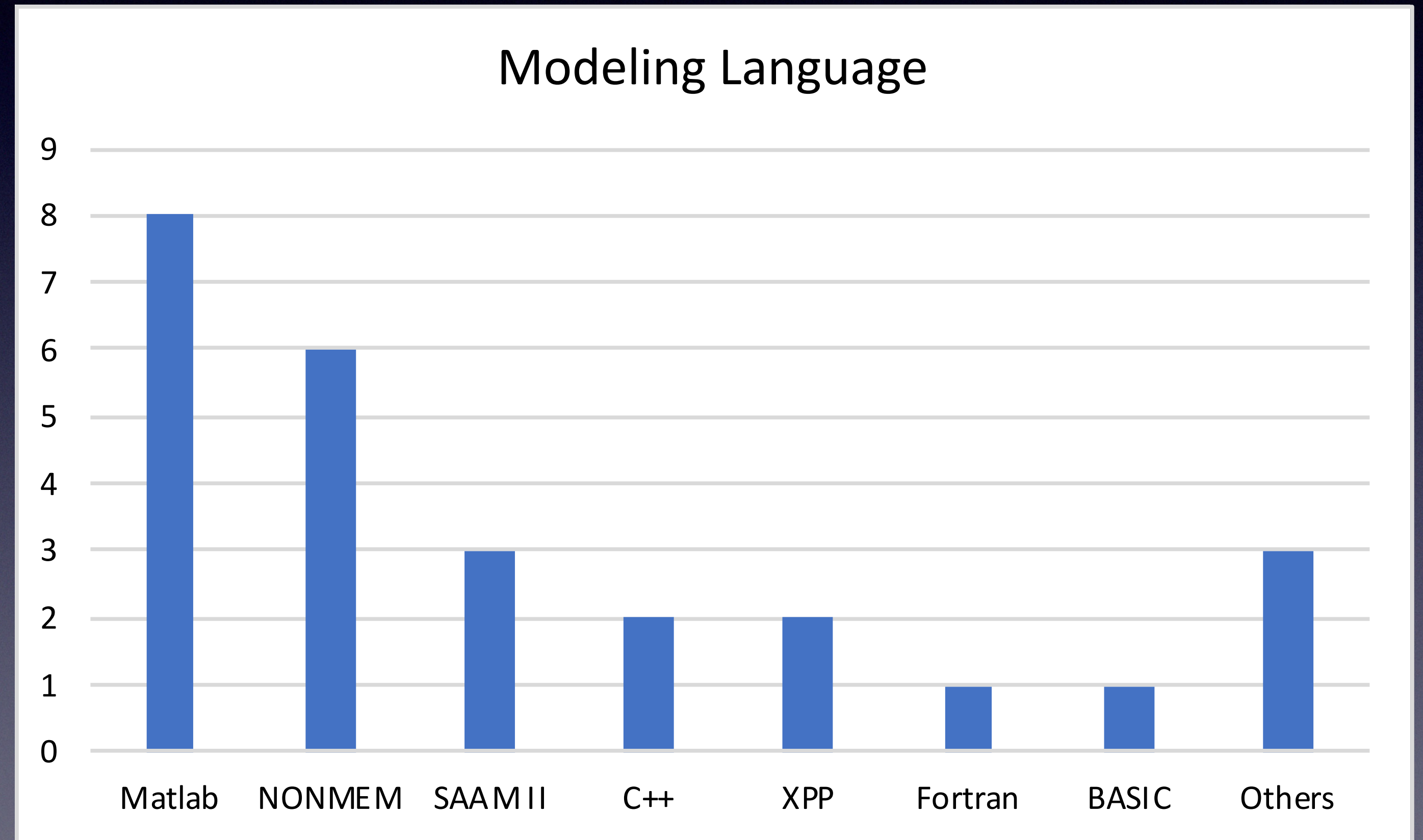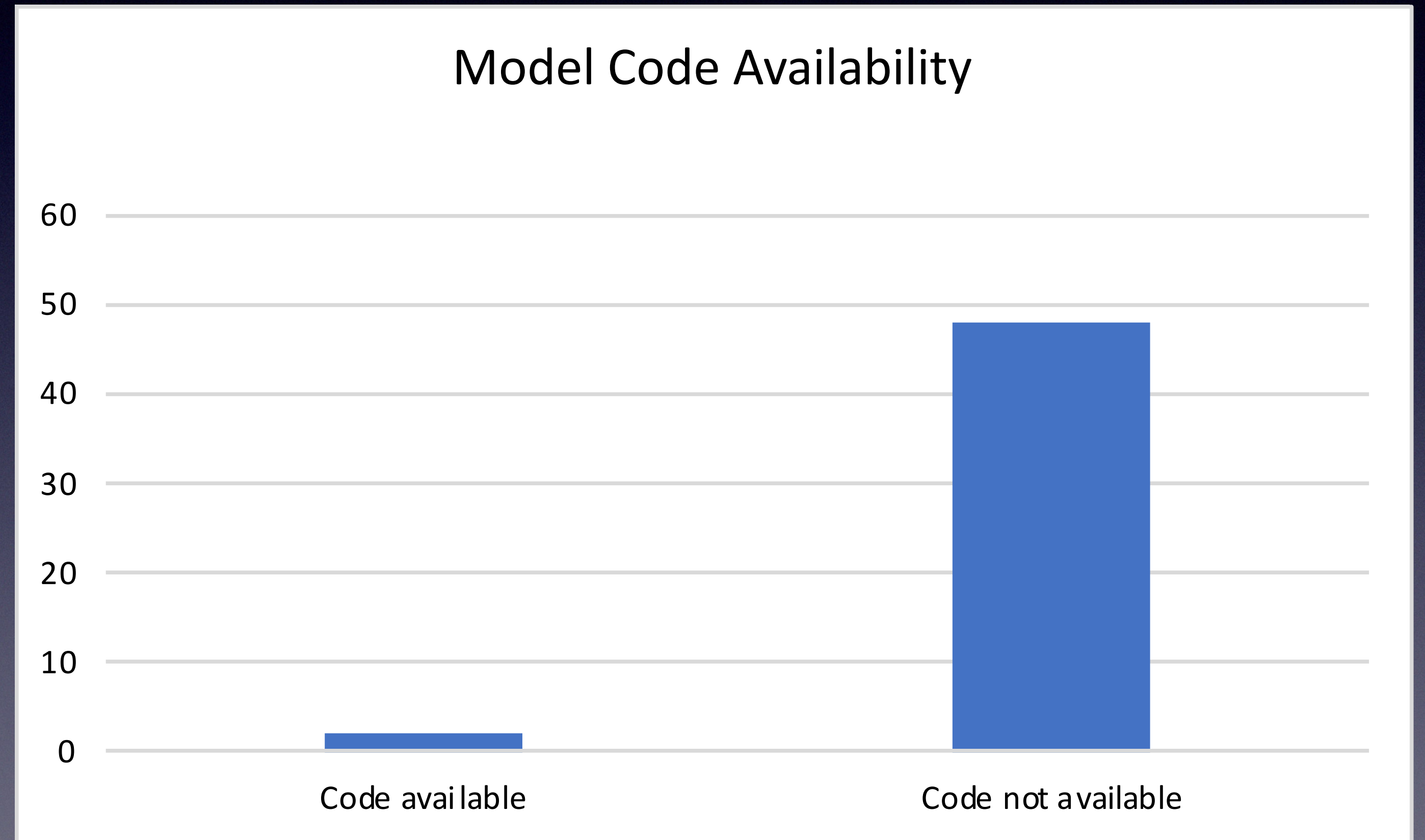
A PHYSIOLOGIC MODEL OF GLUCOSE METABOLISM IN MAN AND ITS USE

TO DESIGN AND ASSESS IMPROVED INSULIN THERAPIES FOR DIABETES

VOL. 1

by

JOHN THOMAS SORENSEN

B.S., University of California, Berkeley

(1978)

SUBMITTED TO THE DEPARTMENT OF
CHEMICAL ENGINEERING IN PARTIAL
FULFILLMENT OF THE
REQUIREMENTS FOR THE
DEGREE OF

DOCTOR OF SCIENCE

at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

April 1985

APPENDIX A: Computer Source Program (Fortran 77)

```fortran
      DATA A,B,XN,H/.048229,.93141,1.,.0079378/
      DATA Y20R,GAMMA/6.3294,.57493/
      DATA XM1,XM2/.007968,.106495/
C
C     PARAMETERS - GLUCAGON MODEL
C
      GNMCR=0.910
      VGN=VVIB+VVIH+VVIP+VKI+VLI+VIP*0.1
C
      ENDIF
C
C     INITIALIZE GLUCOSE MODEL
      IF(NEWDT.EQ.-1) THEN
C***  INPUT FASTING PERIPHERAL VENOUS BLOOD GLUCOSE CONC. (MG/DL)
      Y(6)=CONSTANT(20)/0.84
      Y(3)=Y(6)+PGUF/QVGP
      Y(4)=Y(3)
      Y(1)=Y(3)-BGU/QVGB
      Y(8)=Y(3)-GGU/QVGG
      Y(5)=(1./QVGL)*(QVGA*Y(3)+QVGG*Y(8)+HGPF-HGUF)
      Y(2)=Y(1)-(BGU*TMGB)/VIB
      Y(7)=Y(6)-(PGUF*TMGP)/VIP
      Y(9)=1.
      Y(17)=1.
      Y(21)=0.
C     STORE BASAL VALUES FOR FUTURE COMPUTATIONS
      Y3F=Y(3)
      Y5F=Y(5)
      Y7F=Y(7)
C
C     INITIALIZE INSULIN MODEL
C***  INPUT FASTING PERIPHERAL VENOUS PLASMA INSULIN CONC. (MU/L)
      Y(14)=CONSTANT(21)
      Y(11)=Y(14)/(1.-FICP)
      Y(10)=Y(11)
      Y(12)=Y(11)*(1.-FICK)
      Y(13)=(1./QVIL)*(QVIH*Y(11)-QVIB*Y(10)-QVIK*Y(12)-QVIP*Y(14))
      Y(16)=Y(11)
      Y(15)=Y(14)-((QVIP*TMIP)/(VIP*.1))*(Y(11)-Y(14))
      PIRF=(QVIL/(1.-FICL))*Y(13)-QVIG*Y(16)-QVIA*Y(11)
C     STORE BASAL VALUES FOR FUTURE COMPUTATIONS
      Y11F=Y(11)
      Y13F=Y(13)
      Y15F=Y(15)
```

An Integrated Glucose-Insulin Model to Describe Oral Glucose Tolerance Test Data in Healthy Volunteers

Dr Hanna E. Silber MSc Pharm ✉, Dr Nicolas Frey PharmD, Dr Mats O. Karlsson PhD

The NONMEM code used to implement the flexible input model is presented as follow:

```
DEN1 = THETA(1)
DEN2 = THETA(2)*EXP(ETA(2))
DEN3 = THETA(3)
DEN4 = THETA(4)*EXP(ETA(4))
DEN5 = THETA(5)*EXP(ETA(5))
DEN6 = THETA(6)
DEN7 = THETA(7)
DEN8 = THETA(8)*EXP(ETA(8))
DEN9 = THETA(9)
DEN10 = THETA(10)
DEN11 = THETA(11)
Q1=0
Q2=0
Q3=0
Q4=0
Q5=0
Q6=0
Q7=0
Q8=0
Q9=0
Q10=0
Q11=0
Q12=0
IF(TIME.LE.15) Q1=1
IF(TIME.GT.15.AND.TIME.LE.30) Q2=1
IF(TIME.GT.30.AND.TIME.LE.45) Q3=1
IF(TIME.GT.45.AND.TIME.LE.60) Q4=1
IF(TIME.GT.60.AND.TIME.LE.75) Q5=1
IF(TIME.GT.75.AND.TIME.LE.90) Q6=1
IF(TIME.GT.90.AND.TIME.LE.105) Q7=1
IF(TIME.GT.105.AND.TIME.LE.120) Q8=1
IF(TIME.GT.120.AND.TIME.LE.150) Q9=1
IF(TIME.GT.150.AND.TIME.LE.180) Q10=1
IF(TIME.GT.180.AND.TIME.LE.210) Q11=1
IF(TIME.GT.210.AND.TIME.LE.240) Q12=1
DEN=1+DEN1+DEN2+DEN3+DEN4+DEN5+DEN6+DE
```

Honorable Mention

- Gaetano, et al. (2008). *Mathematical models of diabetes progression.*

"The model's numerical integration, starting with given parameter values, has been implemented in a mixed Matlab (The MathWorks, 1994 –2007) and C/C++ (GCC, Free Software Foundation) environment and **is freely available as a service to academic users through the CNR IASI BioMatLab web site** (18a)."

This site can't be reached

The connection was reset.

Try:

- Checking the connection
- Checking the proxy and the firewall

ERR_CONNECTION_RESET

DETAILS

Reload

What percentage of model publications make model code available?

1.3%

But wait, there's more!

- Even curated models in repositories don't have model code available in the publication!

A New Hope?

- Some of the more recent publications link to BioModels

"The COPASI file, allowing the model to be run and manipulated by others, is **included in the Supplemental Materials** and is also **deposited in the BioModels Database under model ID# MODEL1803300000**."

–Diedrichs, et al. (2018). *A data-entrained computational model for testing the regulatory logic of the vertebrate unfolded protein response.*

Now what?

- Why is this?

  - Lazy modelers? Software corrosion? Publication culture?

- What can we do about it?

  - See John G. and Ion M.'s talks

  - Center for Reproducible Biomedical Modeling

Search Terms

- "Models, Biological"[MH] AND "Computer Simulation"[MH] AND Humans[Mesh] NOT review[ptyp] NOT Meta-Analysis[ptyp] AND (Research Support, American Recovery and Reinvestment Act[ptyp] OR Research Support, N I H, Extramural[ptyp] OR Research Support, U S Gov't, Non P H S[ptyp] OR Research Support, U S Gov't, P H S[ptyp] OR Research Support, U.S. Government[ptyp] OR Research Support, Non U S Gov't[ptyp] OR Research Support, N I H, Intramural[ptyp] OR Validation Studies[ptyp] OR Comparative Study[ptyp] OR Evaluation Studies[ptyp])

- "Models, Cardiovascular"[MH] AND "Computer Simulation"[MH] AND Humans[Mesh] NOT review[ptyp] NOT Meta-Analysis[ptyp] AND (Research Support, American Recovery and Reinvestment Act[ptyp] OR Research Support, N I H, Extramural[ptyp] OR Research Support, U S Gov't, Non P H S[ptyp] OR Research Support, U S Gov't, P H S[ptyp] OR Research Support, U.S. Government[ptyp] OR Research Support, Non U S Gov't[ptyp] OR Research Support, N I H, Intramural[ptyp] OR Validation Studies[ptyp] OR Comparative Study[ptyp] OR Evaluation Studies[ptyp])