Role of systems biology modeling in extrapolating efficacy and safety from adult renal impairment data

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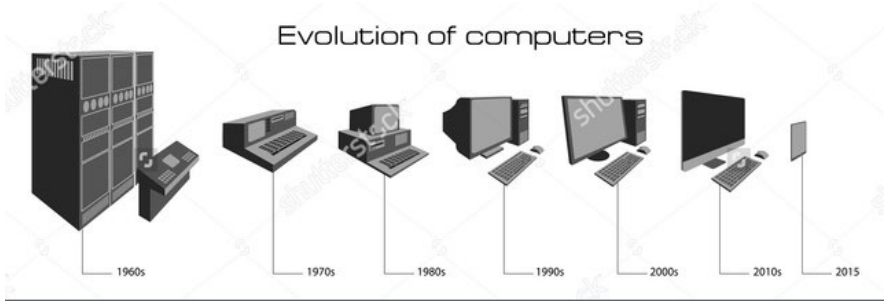
Source: Journal of Medical Systems Biology

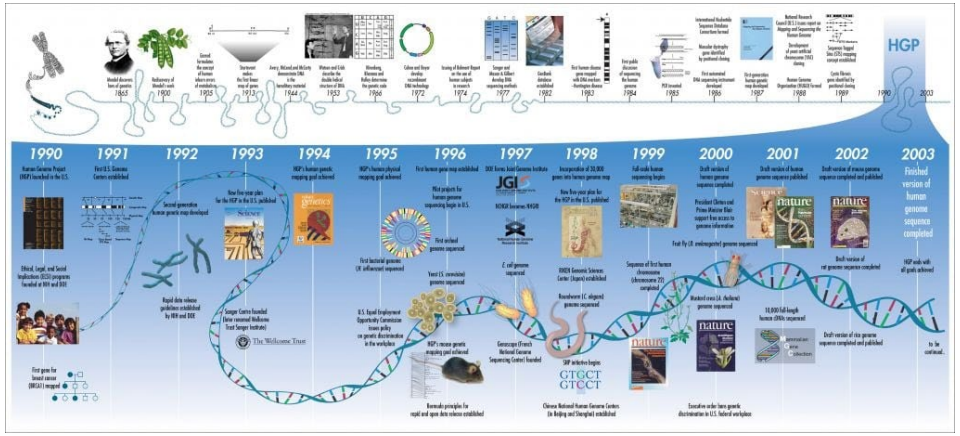
Transforming Discovery and Translational Science Through Systems Biology

Programming Biology via Integration of Computation, Technology and Biology

- Programmable technology has launched a significant technology industry that has revolutionized our society



- The biotechnology industry is now at the cusp and beginnings of similar impact in health and wellness.
  - Enabled by big data and advances in genome science
  - On the heels of the human genome project



- Systems biology / QSP modeling has a growing track record of enabling translational and discovery milestones such as target engagement, mechanism of action and disease, extrapolation, patient segmentation, drug toxicity, …

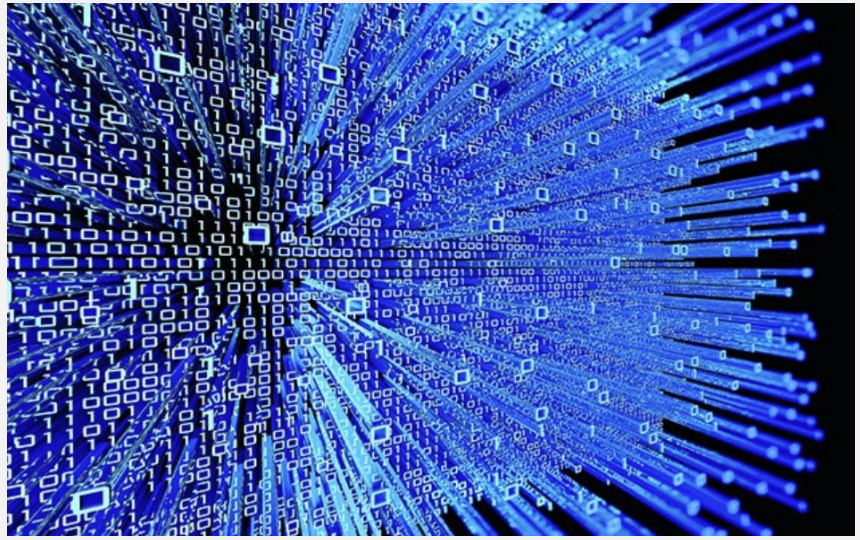
Azer et al. 2021, 2023, Gadkar et al., 2016; Balbas-Martinez et al., 2018; Kaddi et al., 2018; Coletti et al., 2020

Three Key Pillars That Fuel Systems Biology Applications in Drug Discovery and Development

Integration of multimodal OMICs, Target Engagement, Efficacy & Safety data across 3 pillars

1. Computational methods

Discovery and hypothesis generation



- ✓ Text and data mining
- ✓ Modeling
- ✓ Differential expression
- ✓ Pathway analysis

2. Human samples from relevant diseases

With associated clinical metadata to confirm computational predictions; explore molecular signatures of disease progression and patient stratification

- ✓ Translation
- ✓ Disease networks
- ✓ Biomarkers

3. Preclinical models

In vitro and in vivo models for experimental hypothesis testing and characterization of responses to selected compounds

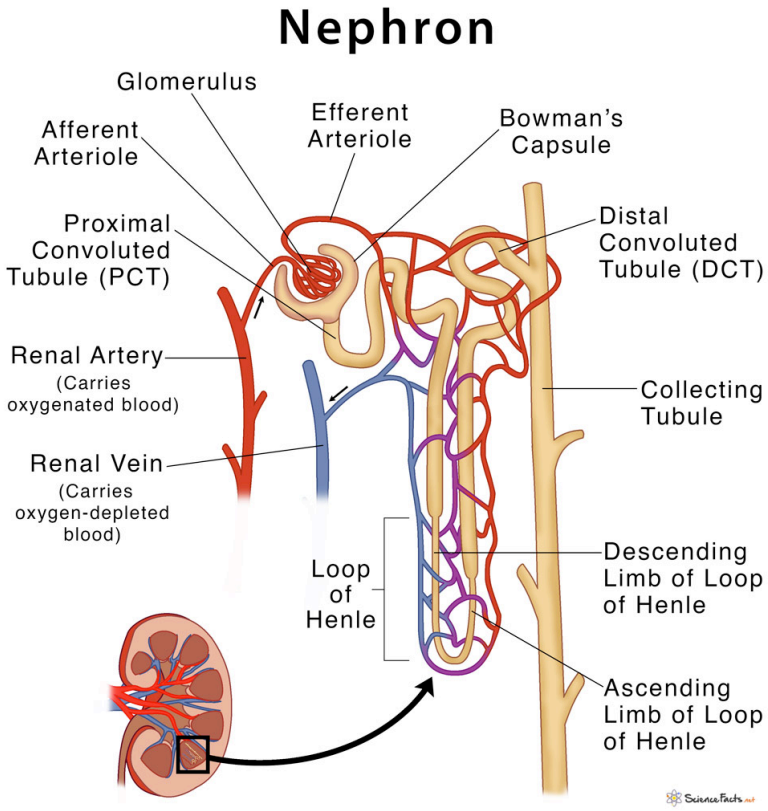
- ✓ Forward translation
- ✓ MOA
- ✓ Treatment effect
- ✓ Dose selection

Azer et al. Front. Syst. Biol., 18

The Kidney has a Central Role in Many Health and Disease Outcomes

Systems biology approach necessary to capture system wide and multi-organ nature of kidney function

- Kidney function is integral to many health and disease outcomes, spanning cardiovascular, metabolic, cancer, and neurological
- Involved in regulation of metabolism, energy, amino acids, cardiovascular system, electrolytes, osmolarity, and waster removal (urea), …
- Kidney regulates the composition of blood plasma –both ways, two high and too low
- About 10^6 nephrons in the kidney, connected in parallel
  - Wide range: 250K to 2M inter-individual
- Primary filter functional unit is the glomerulus



Hoppensteadt , Peskin, Modeling & Simulation in Life Sciences & Medicine
Keener, Sneyd, Mathematical Physiology

Representing Broad Kidney Disease Characteristics Requires a Systems Approach

Systems biology approach necessary to capture system wide and multi-organ nature of kidney function

- Kidney disease
  - primarily driven by hypertension, dysregulated metabolism (glycemic control, pre-diabetes, insulin resistance),
  - Hypertension and diabetes have a synergistic effect on risk of new onset of CKD, and contribute approximately 70% of CKD cases
  - Auto-immune disease, glomerular nephritises, IEMs affecting the kidney,…

- Mechanistic impact of high glucose and blood pressure, and insulin resistance on kidney function includes damage to micro-vasculature (afferent and efferent arterioles), endothelial dysfunction, vascular stiffness, oxidative stress, impact on glomerular pressure
  - E.g. Impact of vasodilation / vasoconstriction (size of afferent and efferent arteries) on rate of filtration

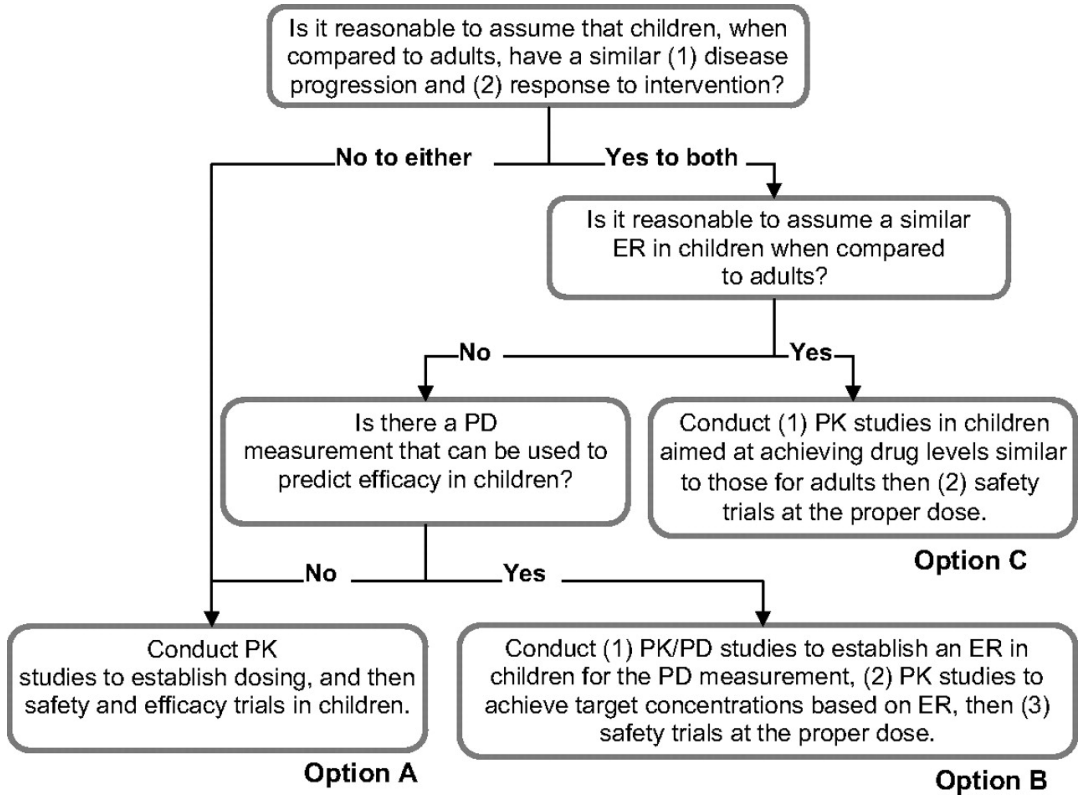
- Systems biology model needed to capture kidney disease attributes and link to filtration capacity
  - e.g. changes in afferent or efferent conductance or resistance

J Clin Hypertens (Greenwich). 2020 Jan; 22(1): 39–46

Extrapolation of Efficacy and Safety of Drugs with Systems Models

Kidney disease and Renal Impairment in Adults and Pediatrics

- Evaluating similarity of disease and drug response by representing mechanism of disease targeted by drugs
- Representing stages of renal function with age and impact on drug clearance or dose
- Assessment of kidney functional measures, variability across populations and age, and mechanistic sources of variability



Yao et al., Pediatrics 11:5

Pediatric extrapolation: Leveraging Systems Biology Modeling for Disease and Response Similarity

- Opportunity to use systems biology modeling / QSP to establish quantitative guidelines for disease and response similarity between adults and pediatrics
  - Establish scope of disease and target biology being modulated therapeutically
  - Identify mechanisms/pathways and biomarkers to be integrated in model to guide disease and response similarity assessments
  - Build virtual population library that covers the space of clinical heterogeneity represented in the disease and age distributions – based on ability to age de-escalate model parameters

Example

Disease Severity	Genotypes	Biomarker	Clinical Endpoints	Prevalence
Mild	…	Distribution x	Distribution 1	X%
Moderate	…	Distribution y	Distribution 2	Y%
Severe	…	Distribution z	Distribution 3	Z%

Sampling of parameter distributions to represent each cohort (adults, pediatrics with different disease and stages of renal development and function

PD variability relative enzyme expression levels from mRNA expression data

PK variability clearance, absorption rate constant, central volume, and bioavailability

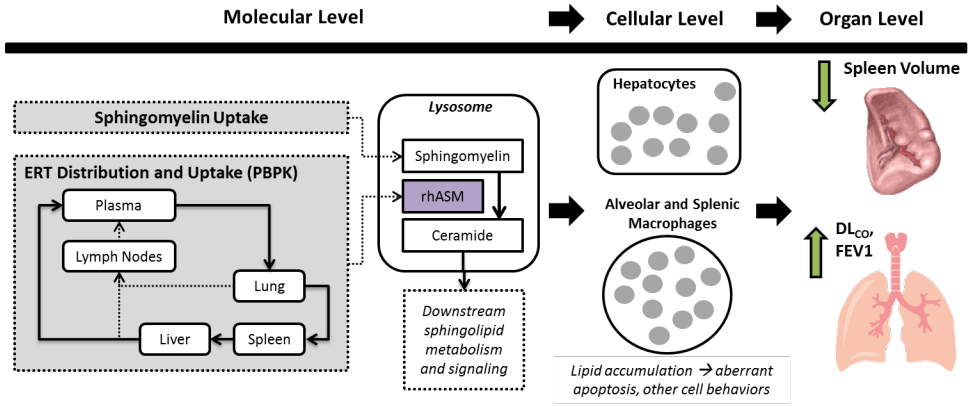
Virtual Patients

QSP Platform Enabled Efficacy Extrapolation to Pediatrics and Accelerating the Path to Pediatric Approval in Rare Disease

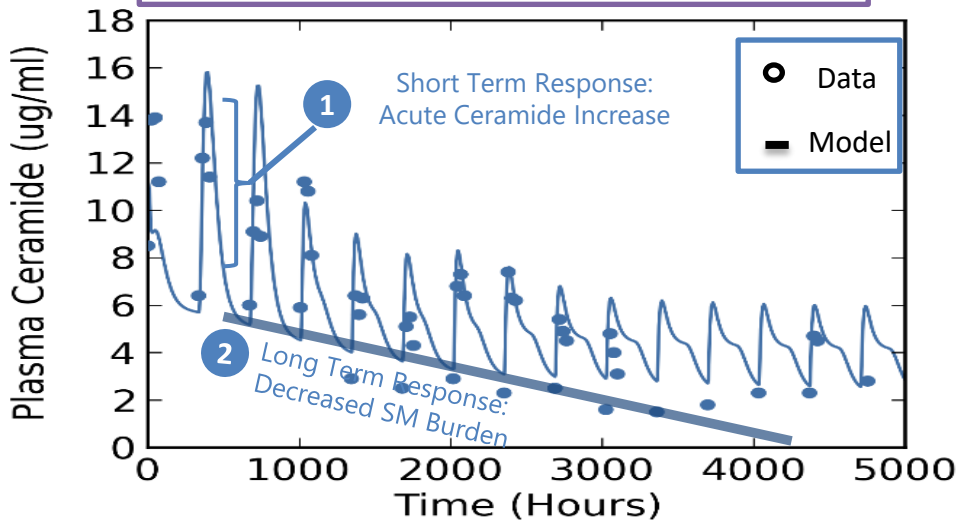
By integrating molecular, cellular and tissue level models with drug effect, the QSP model allowed extrapolation to pediatrics by:

- Investigating differences in disease between adults and pediatrics
- Quantifying the effect of drug on different organs of interest in a heterogeneous and rare disease

Multi-scale QSP Model Description

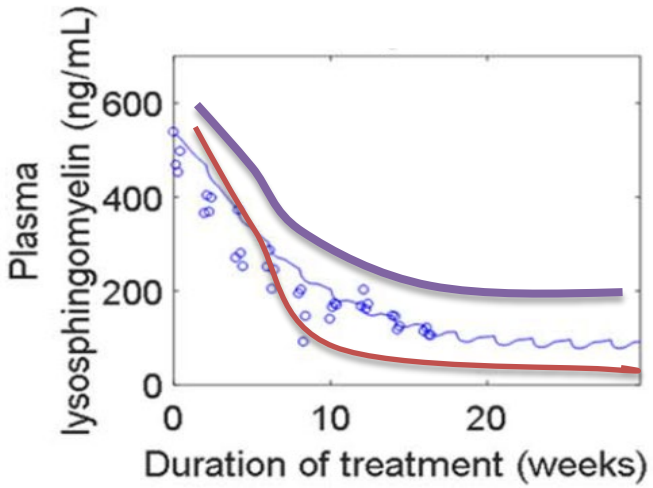


QSP model captures complex Response to Treatment - Validation



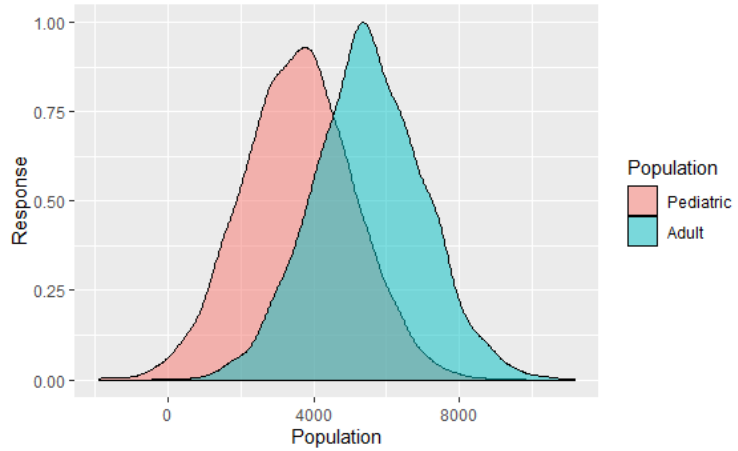
CPT PSP 2018 Jul;7(7):442-452

Application: Extrapolating Efficacy



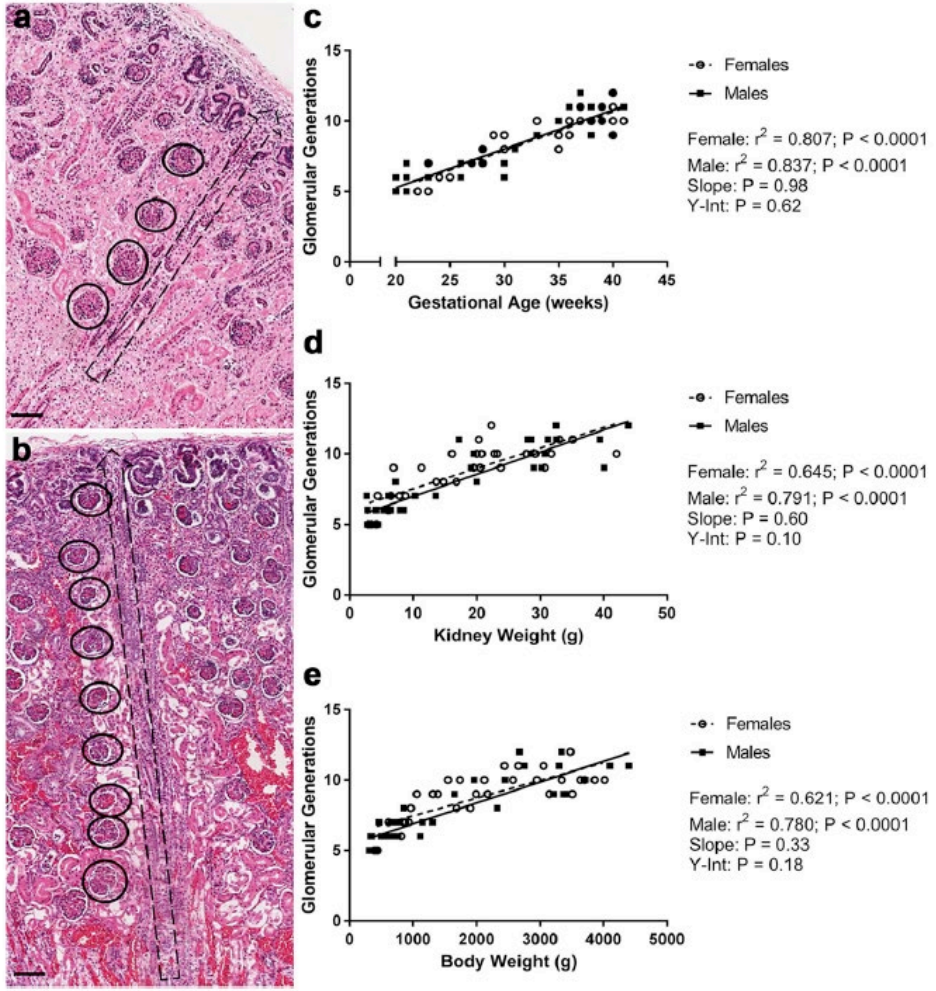
Hypothetical pediatric scenarios

Establishing Similarity Criteria



Accounting for Kidney Filtration Capacity During Growth and Maturation using a Systems Biology Model

Systems Model can be used to estimate drug clearance in neonates



- Model based estimation of drug clearance for different neonatal conditions
- Filtration capacity as a function of age can be accounted for in a systems model
- Account for sources of variability in model:
  - Nephrons formed from 20 week in gestation to term
  - Glomerular generations formed vary widely (8 to 12 generations per kidney)
  - Timing of nephrogenesis cessation

Normal Values of GFR (mL/min/1.73m²)*

Pre-term (25–28 weeks)	
1 week	11.0 ± 5.4
2–8 weeks	15.5 ± 6.2
Pre-term (29–34 weeks)	
1 week	15.3 ± 5.6
2-8 weeks	28.7 ± 13.8
Term	
5–7 days	50.6 ± 5.8
1–2 months	64.6 ± 5.8
3–4 months	85.8 ± 4.8
5–8 months	87.7 ± 11.9
9–12 months	86.9 ± 8.4
2–12 years	133 ± 27

*From Schwartz et al. (1987) and Greene (1991)

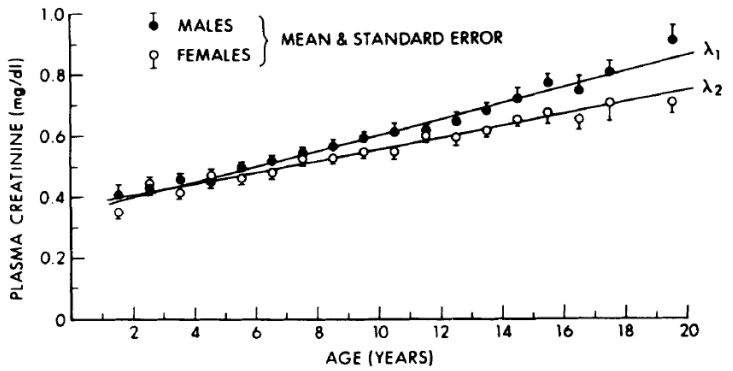


Figure 2. Values of plasma creatinine in normal males and females. From Schwartz et al: *J Pediatr* 88:828–830, 1976.

EBioMedicine 27 (2018) 275–283

Renal Failure, 21(3&4), 283-291 (1999)

Evaluating Kidney Function and Health Requires Understanding of Systemic Homeostasis

- Glomerular filtration is core functional unit of kidney health and disease
- Evaluating kidney function directly via contrast agent studies is infeasible for routine clinical use
  - Can be useful in informing a systems model
- Serum creatinine is a standard marker used to estimate GFR
- Serum creatinine is a by-product of creatine and affected by muscle metabolism and diet
  - Also secreted in PCT
- Cystatin C is alternate protein to estimate GFR, as well as Inulin

CKD-EPI Creatinine Equation (2021)

Expressed as a single equation:

$eGFR_{cr} = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

where:

S_{cr} = standardized serum creatinine in mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.241 (female) or -0.302 (male)

$\min(S_{cr}/\kappa, 1)$ is the minimum of S_{cr}/κ or 1.0

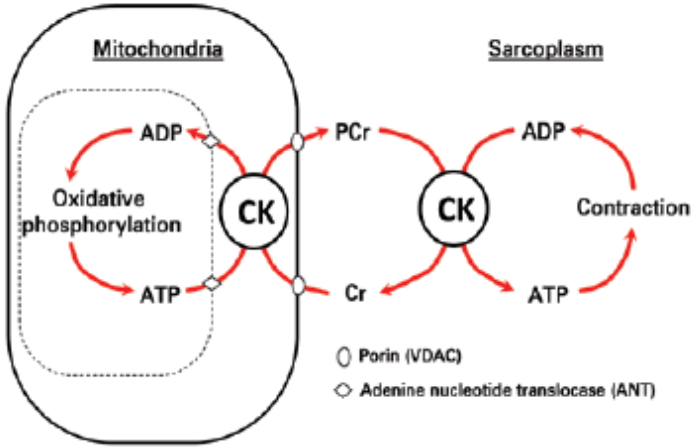
$\max(S_{cr}/\kappa, 1)$ is the maximum of S_{cr}/κ or 1.0

Age (years)

Phospho-Creatine System Integral to Energy Metabolism

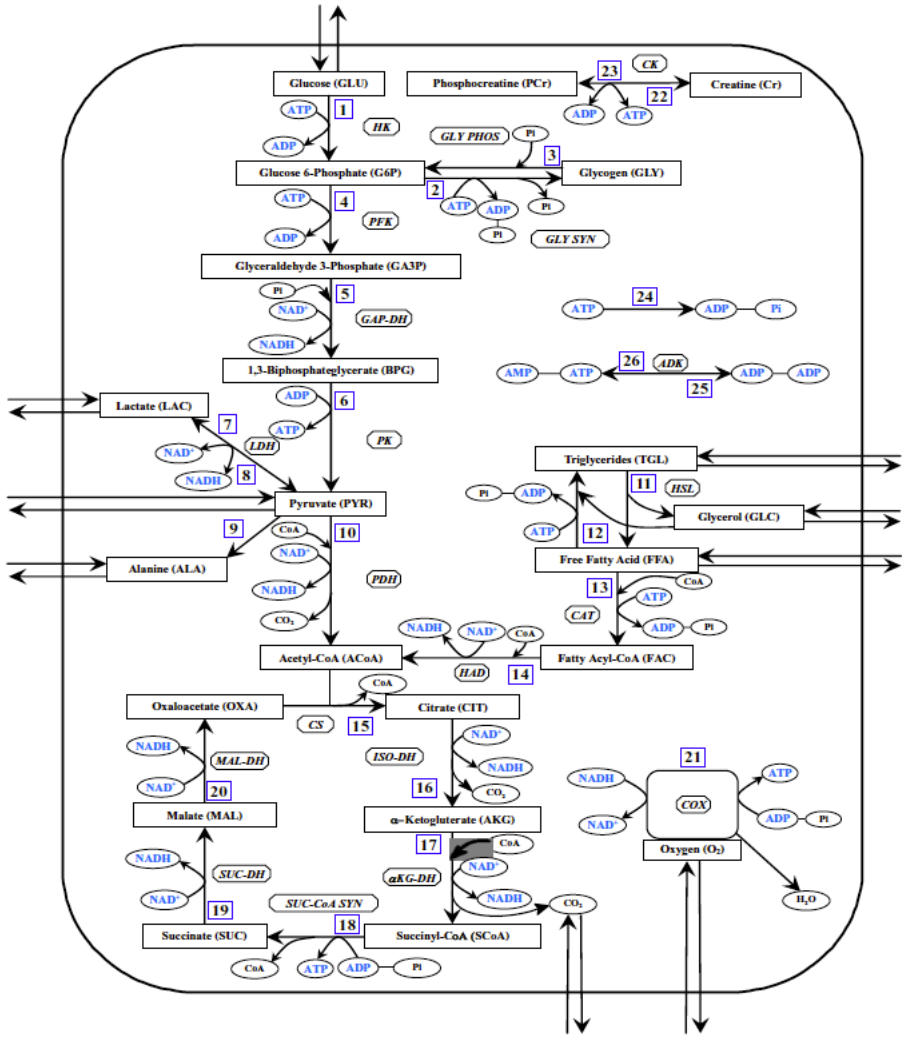
Creatinine is a by-product of creatine and varies with muscle metabolism and energy state

Phospho-Creatine Shuttle



MgADP- + PCr2- + H+ ⇔ MgATP2- + Cr (Equation 1)

Basic Res Cardiol. 1998;93 Suppl 1:102-7. Review
einstein. 2014;12(1):126-31

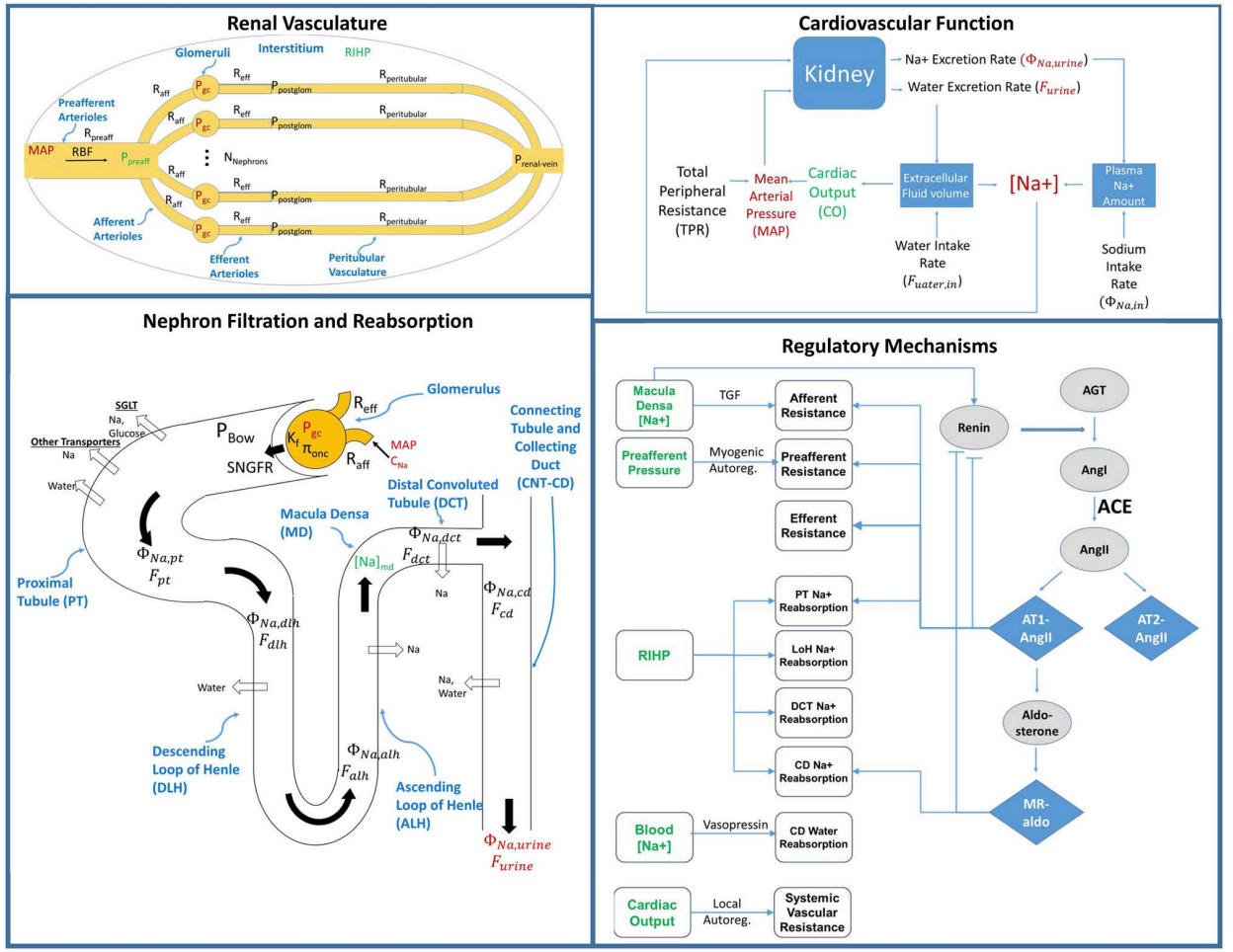


BioMedical Engineering OnLine 2007

Models of Kidney Function & Disease for Extrapolating Efficacy, Safety and Assessment of Kidney Function

Representing Kidney function and level of impairment with age to evaluate impact on drug

- Models to include parameters and processes that represent changes with age, disease, and for evaluating kidney function and drug effect
- Whole kidney function and regulation
- Nephron Filtration and Reabsorption
- Regulatory Mechanisms and cardiovascular function
- Renal Vasculature



npj Systems Biology and Applications (2018) 4:41

Math Biosci. 2015 June ; 264: 8–20

A Systems Model Requires Integrating Diverse Data Sources to Inform the Impact of Kidney Function on Drug Efficacy and Safety

Assessing disease and response similarity between adults and pediatrics	Representing stages, measurement and function of kidney with age
Adult PK/PD data in health and with kidney impairment stages	GFR and other kidney function data in stages of kidney disease, e.g. kidney biomarkers, electrolytes
Benchmark pediatric data in healthy and kidney impairment	Biomarker, demographic data to explain heterogeneity of GFR within population of interest
Omics and biomarker data in adults/adult samples and pediatrics	Mechanistic studies to inform relationship between kidney structure and function and changes with age: Kidney on a chip, in-vitro, in-vivo models, clinical
Target engagement data – clinical POC, preclinical models	Clinical data to validate and qualify models to predict kidney functional outcomes and impact on drug clearance or dose
• Kidney on a chip, in-vitro and pre-clinical models to inform nephrotoxicity: morphological damage, cellular damage/death, kidney injury biomarkers • Precedence with DILI chip and systems biology models • Use model to evaluate impact on metabolites/electrolytes e.g. magnesium, Na, K, … and potential safety concerns	

Conclusions

- Kidney function plays a central role in health and disease, and changes in function affect multiple biological systems
- Systems biology modeling is a critical tool for bridging efficacy and safety, accounting for kidney disease stages and explaining heterogeneity in kidney eGFR measures, as a function of age
- Building this modeling platform requires investment in generating clinical and broad mechanistic data to inform link between kidney function and structure and changes with age and impact of drugs