Clinical Results of Applying Systems Thinking – Part 1

Jim Rogers, Advance Management Group

Edward Gallaher, Ph.D.

Agenda for Part 1

- Chronic Kidney Disease and Related Matters
- Anemia: Critical Concern for Dialysis Patients
- Current Drug Administration Protocols
- Learning About Hemoglobin Cycling
- The Science: Erythropoiesis (“Red” + “Making”)
- Model Iterations
- System Implementation and Results
- Messages to Systems Thinkers
- Introduction to Part 2: Biophysical System Dynamics

CKD, ESRD, and Hemodialysis

- Chronic Kidney Disease (**CKD**): Any disease that leads to a permanent loss of kidney function.

- Kidney function is measured by Glomerular Filtration Rate (**GFR**).

- End Stage Renal Disease (**ESRD**): a complete/near complete failure of the kidneys to concentrate urine, excrete wastes, or regulate electrolytes.

- Hemodialysis (**HD**) is one of several treatment options for Renal Replacement Therapy (**RRT**).

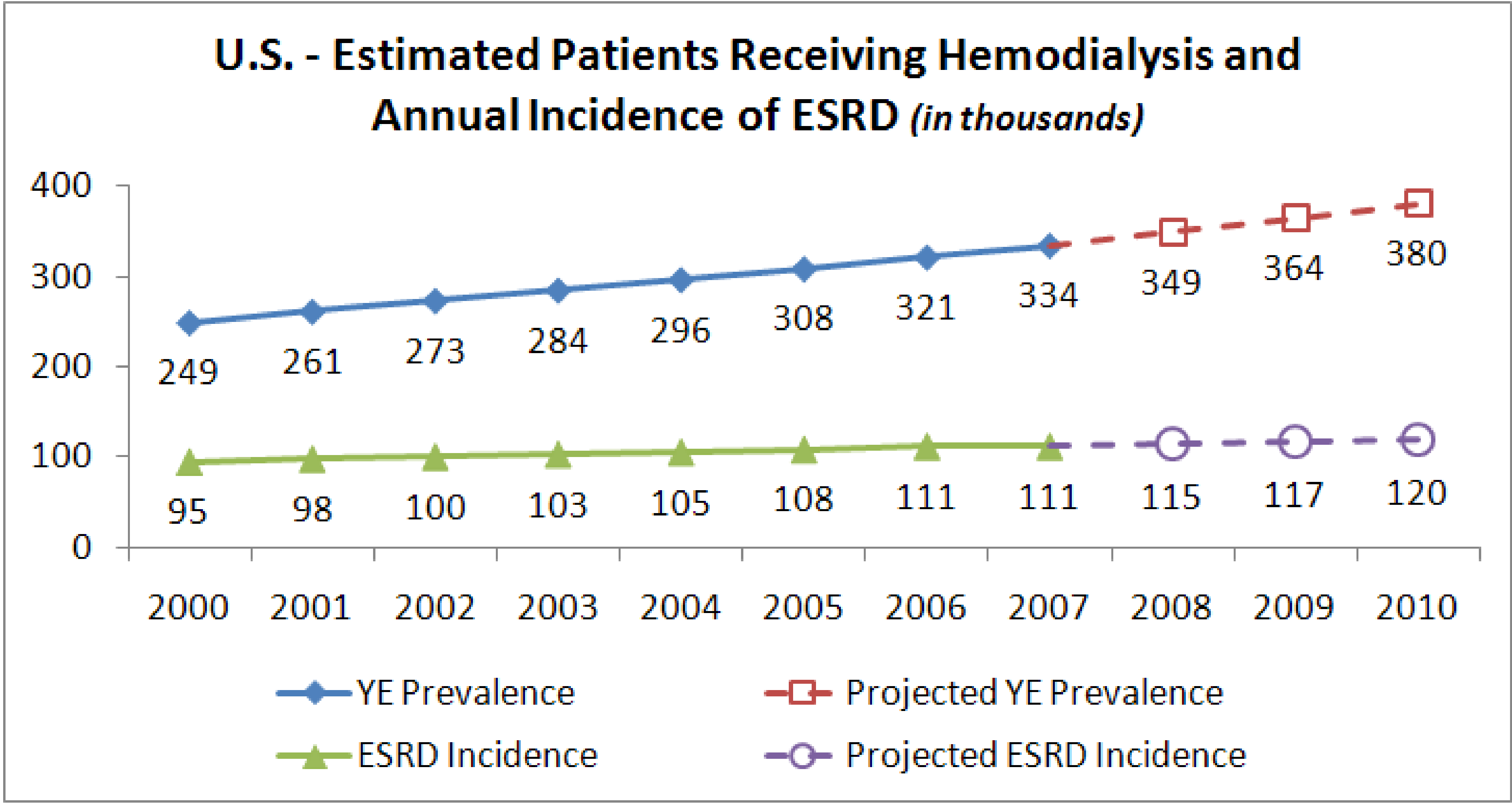
- **HD** filters waste, removes extra fluid, and balances electrolytes by filtering blood with machines.

- Patients on dialysis are categorized as having ESRD, irrespective of the level of GFR.

CKD, ESRD, and Hemodialysis

- CKD is classified into five stages:

Stage	Description	GFR (ml/ min/ 1.73 m^2)
1	Kidney damage with GFR with slightly below normal GFR*	≥ 90
2	Kidney damage with mild reduction of GFR	60-89
3	Moderate reduction of GFR	30-59
4	Severe reduction of GFR	15-29
5	Kidney failure (ESRD) , or on dialysis	< 15
*Normal adult GFR is approximately 100 to 120.		



Scratchpad note: 380,000 Dialysis Patients in 2010 x $30,000 per patient = $11.4B.

For Dialysis Patients:

- Damaged Kidneys do not Synthesize Erythropoietin.
- Anemia is a Prime Concern.
- ESA's Are the Most Effective Anemia Management Tool.
- ESA Protocols Aim to Maintain Hgb in a Target Range of 10 to 13.
- Here is an Example of a Typical Monthly ESA Protocol:

Current Hemoglobin Level	Intervention
Dose Change Previous 30 Days	Continue Current Dose for 30 Days
Hgb <= 10.5	Increase By Up To Two Strengths
10.6 < = Hgb < = 11.9	Increase By One Strength
12.0 <= Hgb <= 12.9	Continue Current Dose
Hgb > = 13.0	Decrease Dose By One Strength

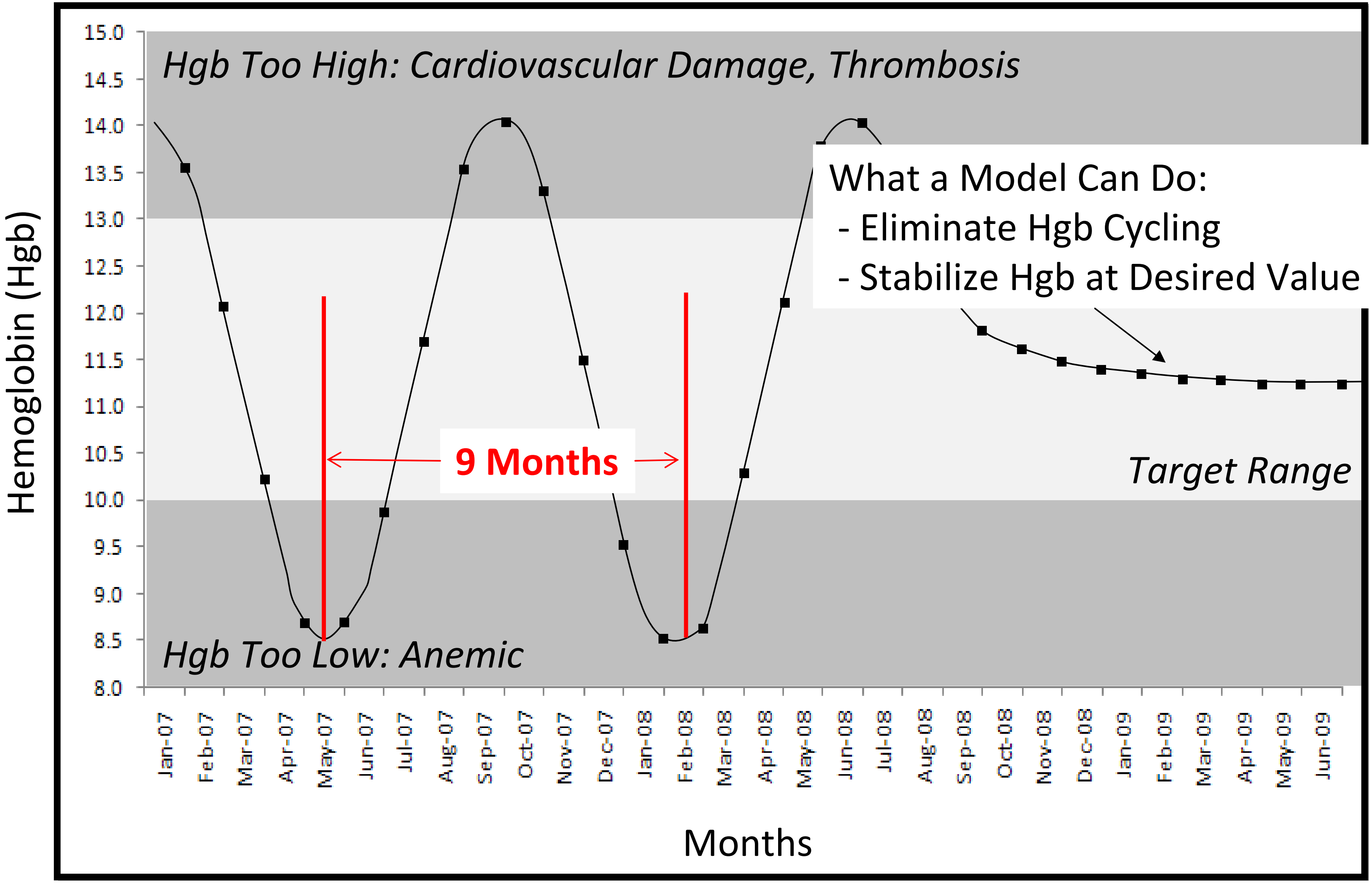
From a Systems Thinking Perspective, What Might be the Limitations of the Mental Models Supporting Current Protocols?

When Practitioners "Get Data", What Do They Get?

Sample Screenshot of a Practitioner's Workbench:

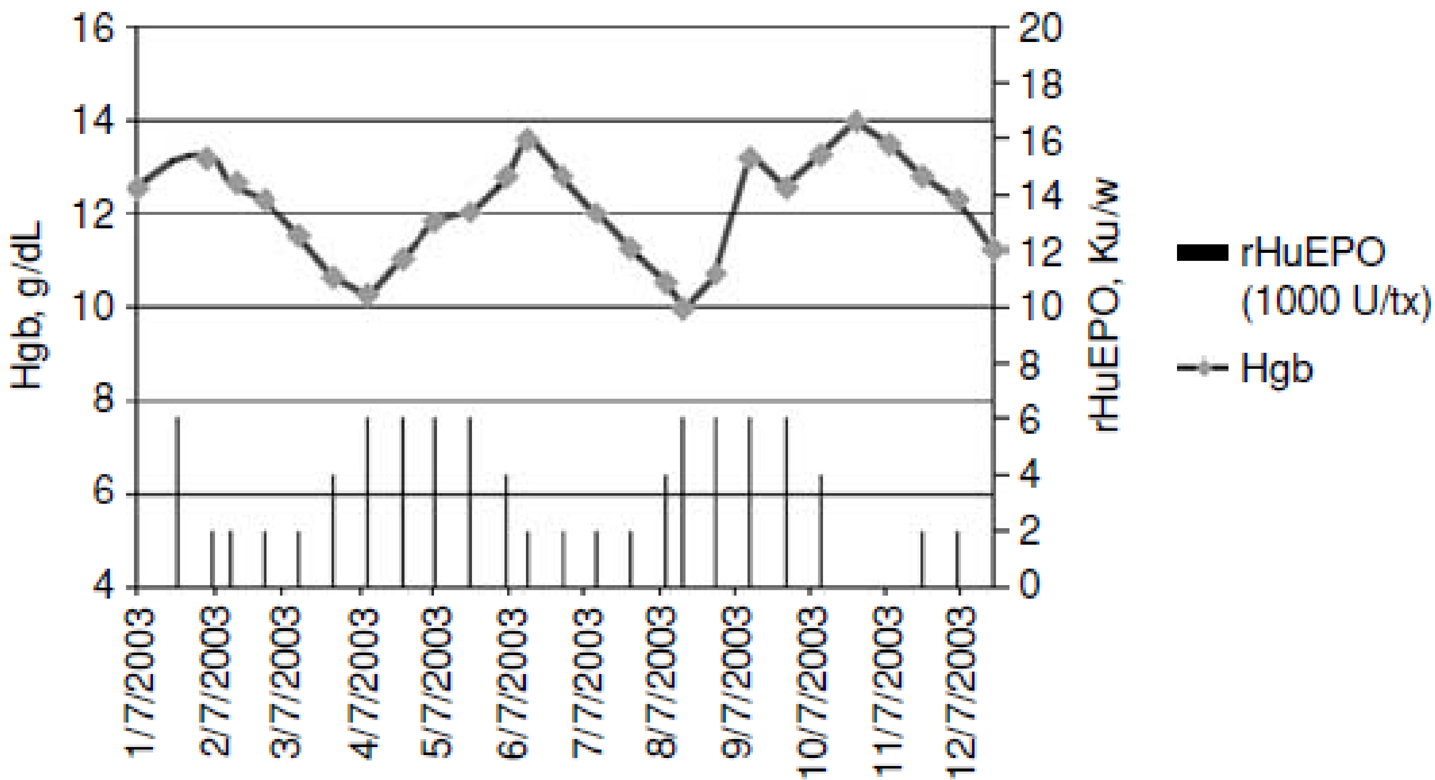
	Sep	Aug	Jul	Jun	May	Apr	
Albumin	3.8	3.5	3.8	3.8	3.7	3.8	→ Kidney Function
AST	15.0	14.0	16.0	17.0	19.0	20.0	→ Liver Disease
Bicarbonate	24.0	25.0	23.0	24.0	22.0	21.0	→ Electrolytes
Ca x P	38.6	27.3	45.4	36.1	44.8	41.8	→ Bone Disease
Calcium	8.4	8.8	8.4	8.6	8.0	8.2	→ Bone Disease
Creatinine	5.6	4.7	4.8	5.1	5.1	5.6	→ Kidney Function
eKt/V	1.5		1.7	1.7	1.6	1.7	→ Dialysis Adequacy
Ferritin	254.0		426.0			230.0	→ Anemia
Hematocrits	37.6	40.6	38.0	35.1	38.9	37.7	→ Anemia
Hgb	**12.2**	**13.3**	**12.7**	**12.1**	**13.0**	**12.8**	→ Anemia
Iron	33.0		65.0			59.0	→ Anemia
MCV	96.6	96.5	97.9	99.0	101.3	100.0	→ Anemia
Phosphorus	4.6	3.1	5.4	4.2	5.6	5.1	→ Bone Disease
Platelet	492.0	362.0	294.0	286.0	326.0	323.0	→ Cardiovascular
Potassium	4.5	5.1	4.8	4.6	4.6	4.5	→ Electrolytes
PTH			2.5			2.7	→ Bone Disease
RBC	3.9	4.2	3.9	3.6	3.8	3.8	→ Anemia
Sodium	141.0	142.0	143.0	142.0	140.0	143.0	→ Electrolytes
Transferrin Saturation	22.0		37.0			34.0	→ Anemia
URR	78.0		83.3	83.7	80.0	82.7	→ Dialysis Adequacy
WBC	12.1	11.2	11.7	9.5	9.9	11.3	→ Infection
More…							→ Whatever…

What Patients Typically Experience with Current Protocols



Hgb Cycling Among Dialysis Patients

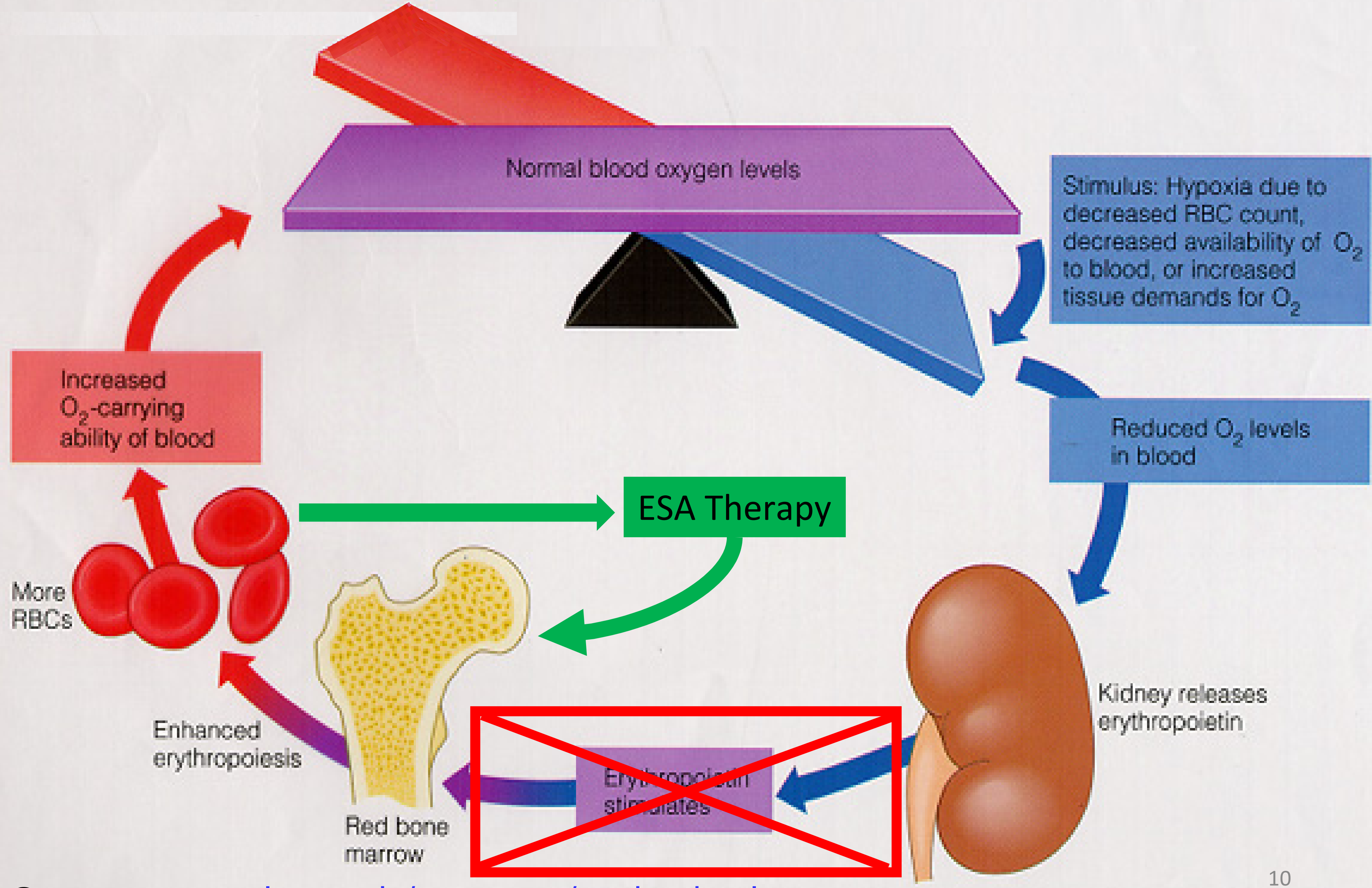
"Treatment with recombinant human erythropoietin (**rHuEPO**) has been a major advance for the management of anemia in patients on hemodialysis. Therapy, however, is often observed to be associated with recurrent cyclic fluctuations in hemoglobin levels." [1]



Graphic example of hemoglobin cycling in a 59-year-old diabetic man, showing both Hemoglobin and recombinant human erythropoietin (**rHuEPO**) dose. [1]

[1] Hemoglobin Cycling in Hemodialysis Patients Treated with Recombinant Human Erythropoietin, Steven Fishbane and Jeffery S. Berns, Kidney International, Vol. 68 (2005), pp. 1337–1343.

Erythropoietin mechanism for regulating the rate of erythropoiesis

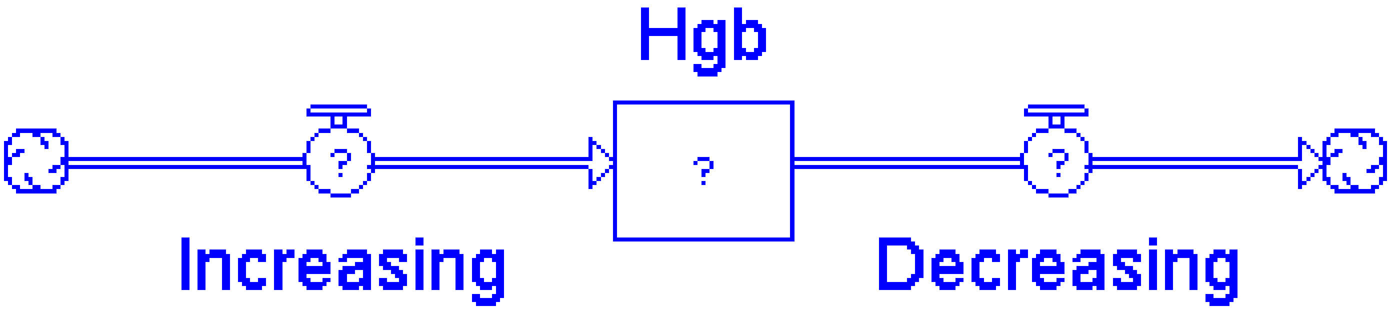


Source: www.tarleton.edu/~anatomy/erythro.html

Red Blood Cell Fact Sheet

- Transport O_2 to the body and CO_2 from the body to the lungs.
- Complete one cycle of circulation every 20 seconds.
- Develop in the bone marrow over a 15-20 day period.
- Circulate for 100–120 days in the body before their components are recycled.
- Produced at a rate of 2.4 million per second.
- Adults have roughly $2–3 \times 10^{13}$ (20-30 trillion) RBC's at any given time.
- Comprise one quarter of the total human body cell number.
- Each RBC contains approximately 270 million hemoglobin molecules, each carrying four heme groups
- These molecules provide the mechanics for O_2 and CO_2 transport.

Model 0

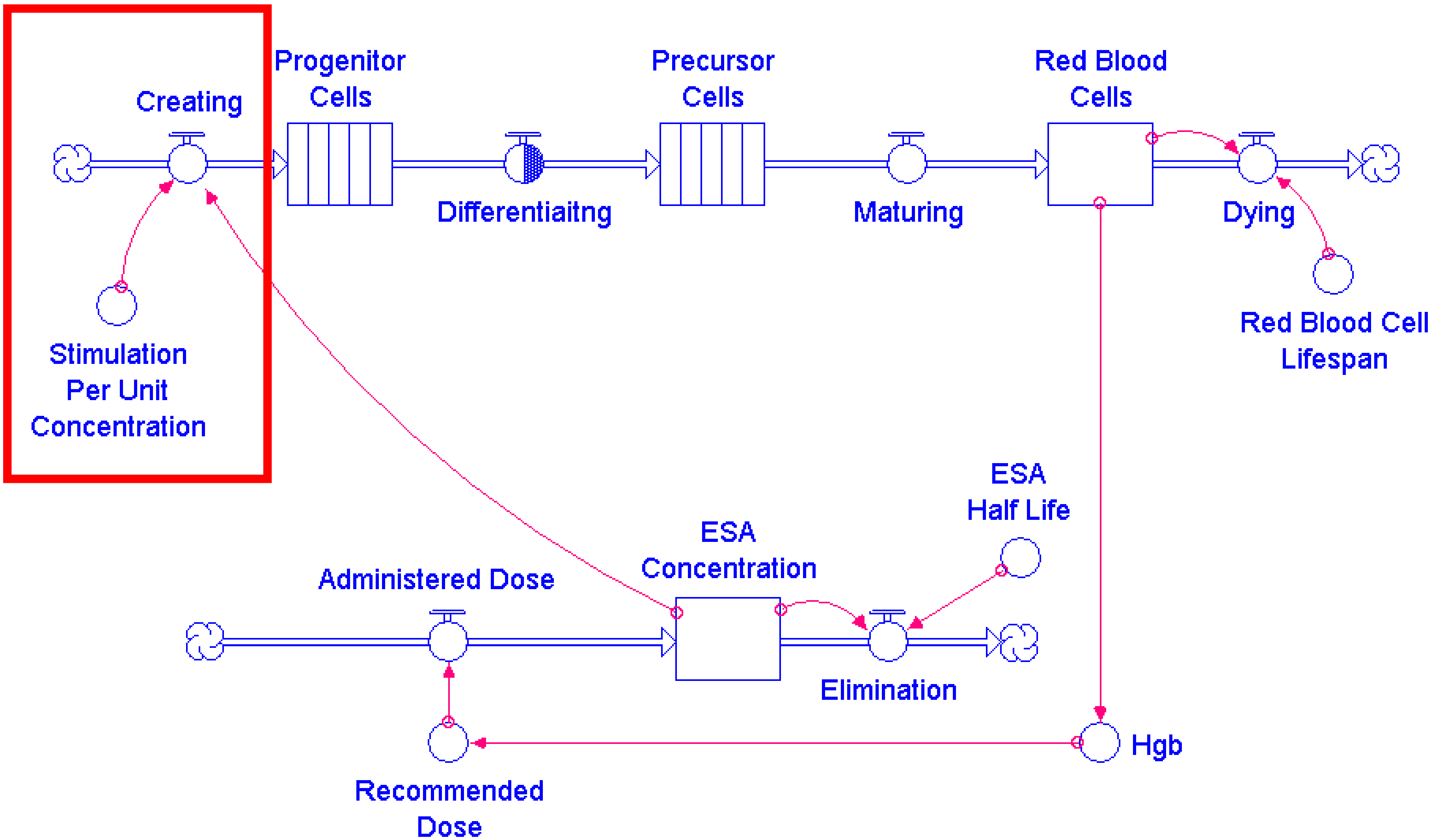


How is Hgb Measured?

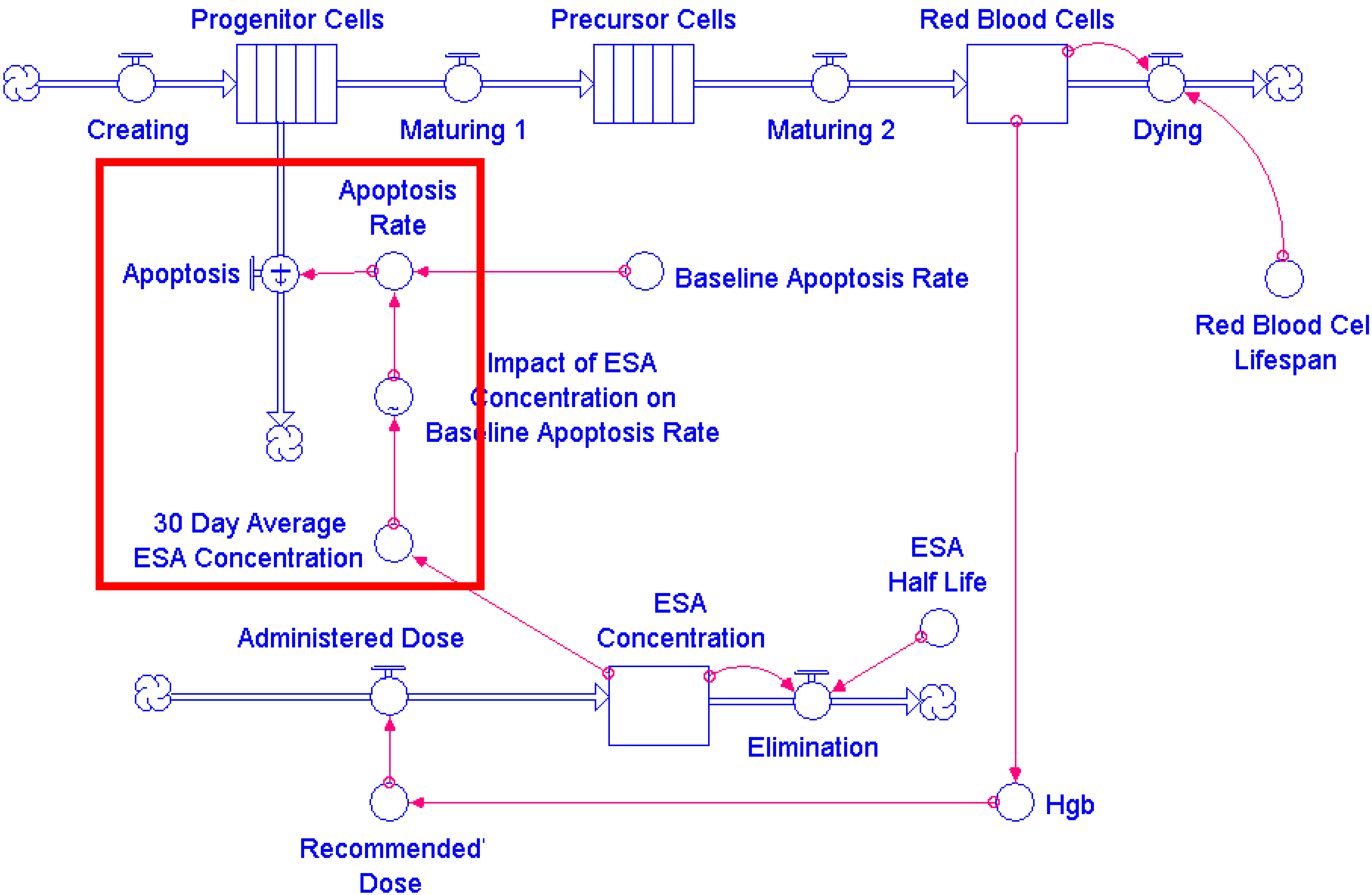
What Causes Hgb to Increase?

What Causes Hgb to Decrease?

Modeling Erythropoiesis: Iteration 1

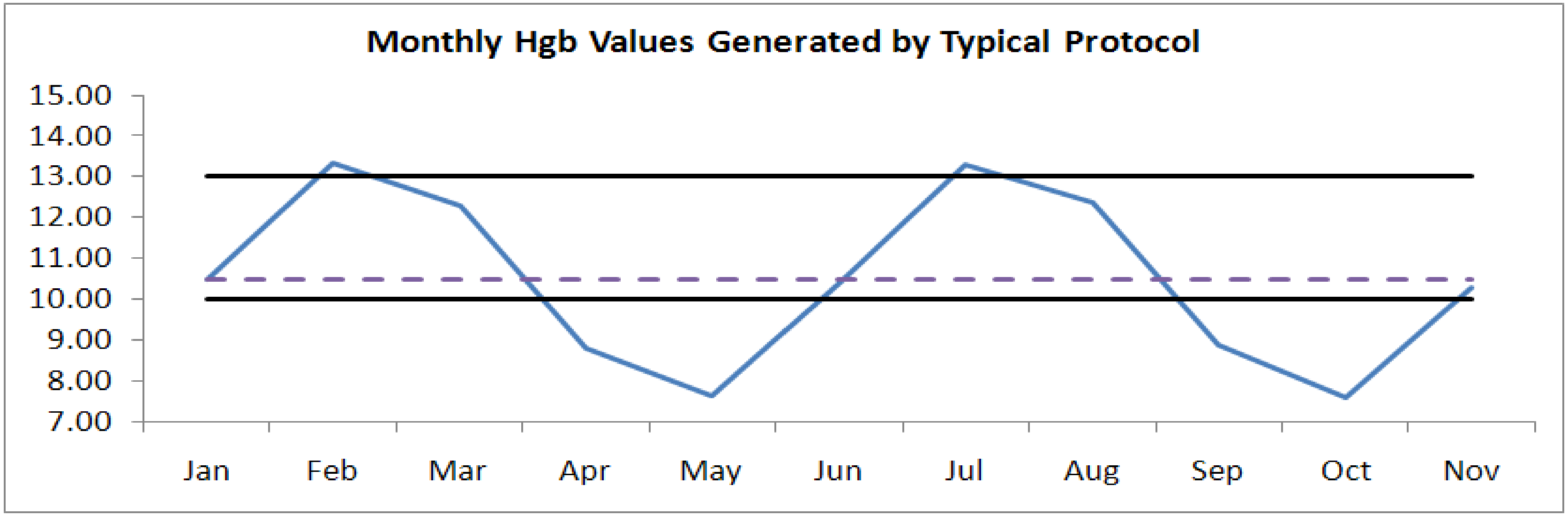


Modeling Erythropoiesis: Iteration 2

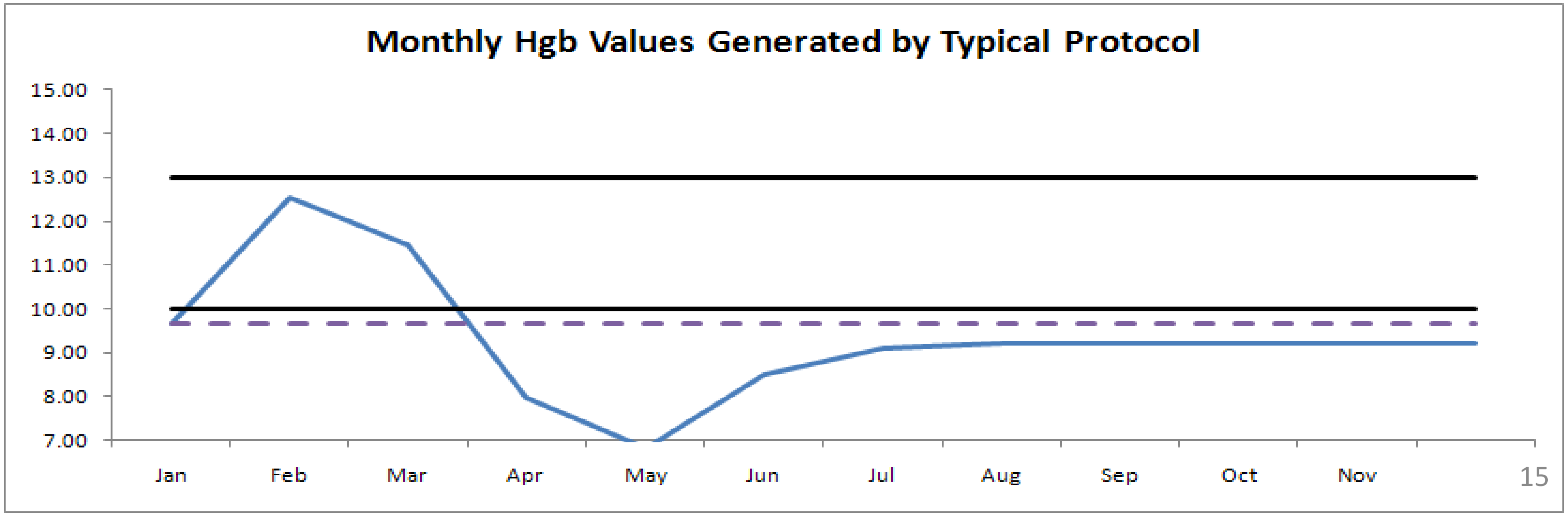


Using the Iteration 2 Model We Learned That:
The Typical Protocol Generates Two Types of Outcomes

Type 1: Oscillation About Some Center Line:



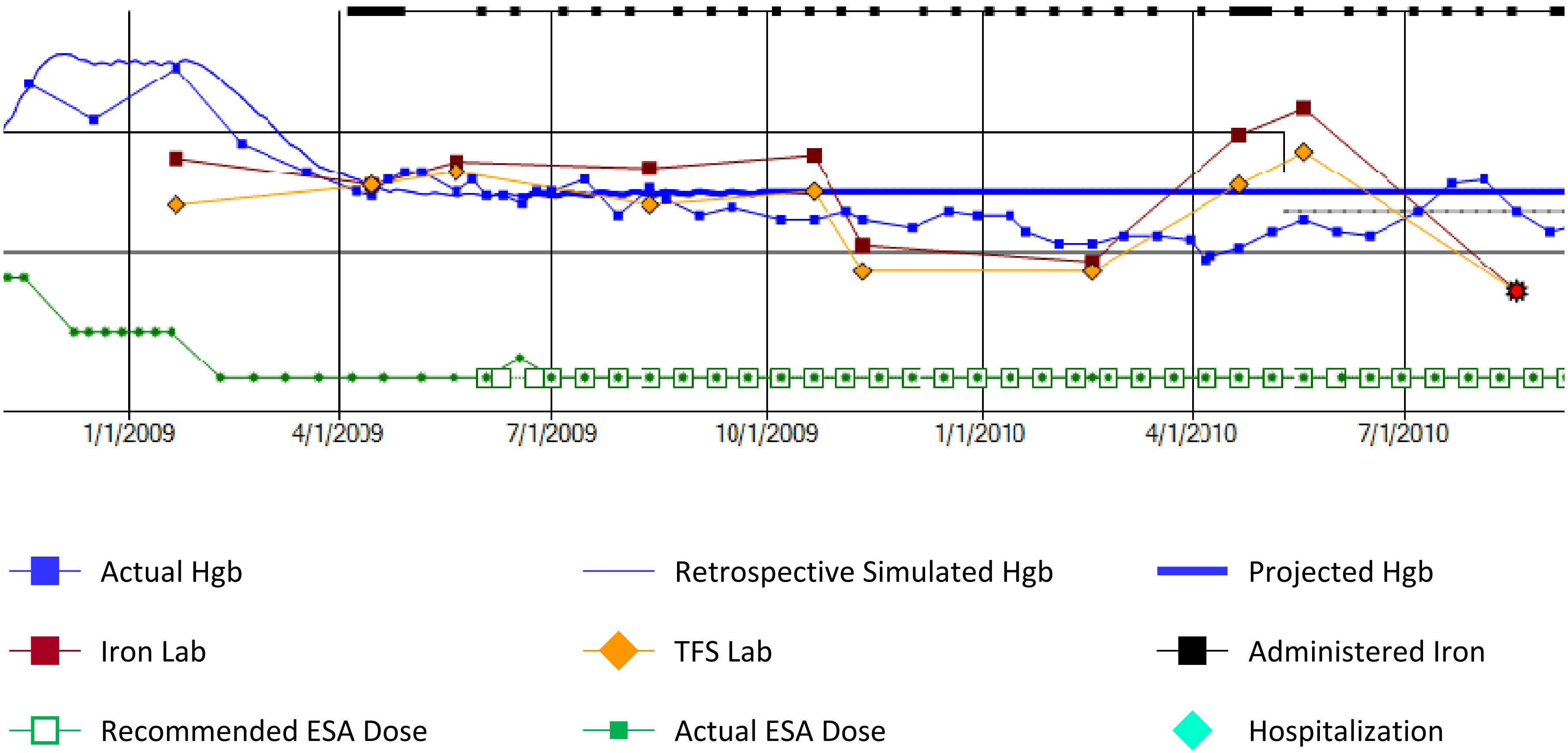
Type 2: Accidental Stabilization at Some Value



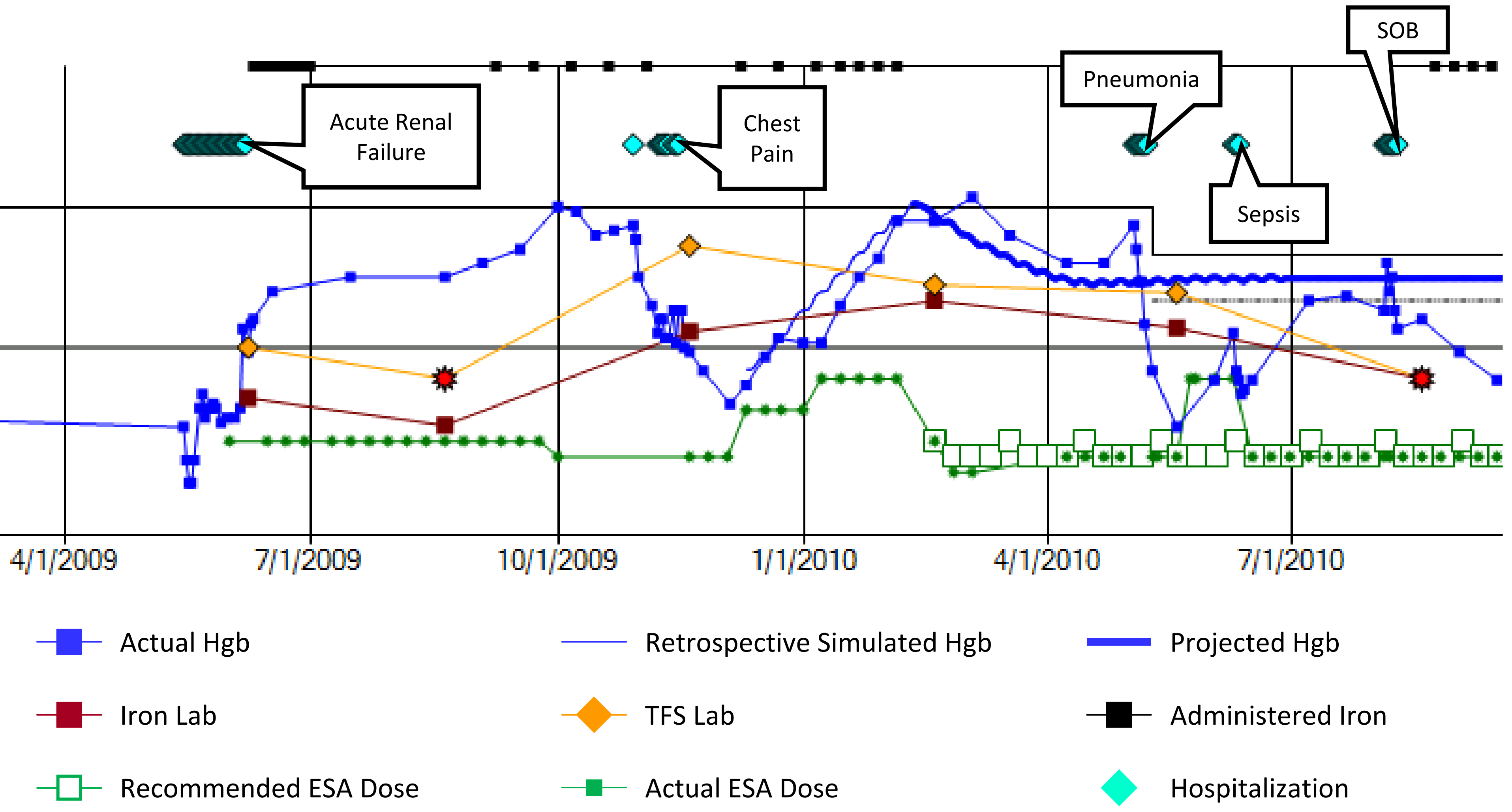
Implementation

- Tested a Pilot Group of Patients in a 12 Week Study
- Challenged the Results by Looking at 18 Patients for Whom the Model "Did Not Work"
  - 13/18 had emergent medical conditions
  - 4/18 had dose misadministrations
  - 1/18 was unexplained
- Conducted a Second Pilot of 15 Patients with Same Results
- Used the "Model Based Protocol" for The Remaining Patients at the Test Site
- Deployed the "Model Based Protocol" Throughout the Organization
  - 600 Patients
  - 450 Applicable to "Model Based Protocol"
  - 75 Patients Will Become Applicable After Exogenous Factors Have Been Stabilized (Iron Repletion)
- Currently Monitoring 600 Patients Using Systems Thinking

Example 1 - The New Work Bench: What They See is What They Got



Example 2 - The New Work Bench: What They See is What They Got



The Prototype "System"

- Consists Of:
  - A Single Erythropoietic Simulation Model
  - Methods to Deliver Batches of Individualized Recommended ESA Prescriptions
  - Weekly Data Collection Tools
  - Database and Reporting System To Monitor Weekly Progress for All Patients in the System
  - Individualized Behavior Over Time Charts of Key Variables
  - Feedback and Reporting System to Adjust Prescriptions as Required
  - Analytic Tools to Report on Progress and Areas for Improvement

The High Performance Obtained with a Model Based Protocol Have Been Sustained and Enhanced Over the Past Year

- Version 2 of the erythropoietic simulation model is currently being tested.
- Plans to commercialize a product or service are in play.
- Academically oriented medical centers are key future partners.

Messages to Systems Thinkers

- Follow the Data
  - What is Flowing?
  - What is Accumulating?
  - What Moderates What?
- Enlist Motivated Learners and Help Them Achieve Personal Results
- Let Successive Iterations of the Model Inform You
  - Articulate Successive Versions of the Model to Engaged Participants
  - Challenge, Validate, and Revise the Model
  - Test, Test, Test
- Engage Networks of Interested Participants
  - Articulate Learnings in Terms of What New Players Understand
  - Engage Varying Viewpoints
- Translate Verified Simulation Results to Business Results
  - Regardless of the Current Measurement System, Make the Case
  - Anticipate Organizational Barriers to Fundamental Change
- Overcome Barriers with Understandable Examples , Create an Expansion Path
- The Model Building Process Will Lead You to Actionable Results!
- The Process is Widely Applicable.

Part 2, Biophysical System Dynamics, Will Address the Following:

- How Do I Establish Boundaries for an Effective Model?
- What Level of Aggregation is Effective?
- How do I Identify Model Parameters?
- What Data Do I Need and at What Frequency?
- How Do I Build a Generic, Yet Specific, Model?
- When I Get to Spin Mode, What Do I Do?