Chapter 10 deals with homeostasis. It shows that causal loop diagrams are an excellent way to depict the feedback in a physiological system. These diagrams are a good tool for communication, but what about the rest of the system dynamics method? You are probably wondering if stock-and-flow modeling can be used to improve our understanding of physiological systems.

System dynamics simulation modeling can certainly contribute in physiology, as demonstrated by previous studies summarized below. The method makes an important contribution because of the emphasis on feedback and the ability to capture nonlinear relationships through numerical simulation. This document reviews previous applications and then turns to a step-by-step modeling example of shivering, adapted from shivering model in Douglas Riggs' text on "Control Theory and Physiological Feedback Mechanisms."

His model simulates the role of shivering to control body temperature. I'll follow the suggestion from chapter 13 to build and test a system dynamics model in iterative fashion. You will see two models here. You can take on additional changes as part of the exercises.

**System Dynamics Applications to Physiology**

Gallaher (1996) explains that many biomedical problems (such as diabetes, hypertension and drug tolerance) are fundamentally problems of biological control systems. He argues that system dynamics is ideally suited for the analysis and interpretation of these systems, and he sets forth guidelines to promote a field of "Biological System Dynamics."

Gallaher was not the first author to argue for system dynamics applications in physiology. Bush (1985) described a physiological model in the opening issue of the *System Dynamics Review*. He used system dynamics to study plasma water loss from patients burned over a large portion of their body. The model used one stock to simulate plasma water in the body and a second stock to keep track of the reservoir of prescribed water used for intravenous treatment. The first article is a good opening example since the model is limited to two stock variables. The model was published as a first step toward a detailed study of burn patients which might lead to better guidelines for fluid therapy in general and possibly to special rules to be followed in well defined circumstances.

Hansen and Bie (1987) describe a whole-body model of the micro vascular and lymphatic transfer of fluid and plasma protein in dogs. The model is based on currently accepted physiological concepts and was designed so that each parameter has a direct physiological counterpart, thus making experimental evaluation possible. The model used four stocks to keep track of plasma water, interstitial water, lymphatic water and cellular water. Three stocks were used to keep track of plasma protein, interstitial protein and lymphatic protein. The final three stocks simulated the plasma sodium, interstitial sodium and lymphatic sodium. The model simulations showed good agreement with experimental data from conscious dogs in steady state during two protocols of acute hypotonic over hydration.
Additional examples include the work by Sturis (1991), Smith (1996) and Hargrove (1998). Sturis explains a computer simulation model to illuminate the possible causes of ultradian oscillations in human insulin secretion. These are long cycles (around 120 minutes) that may appear in humans during continuous enteral nutrition, after meal ingestion and during constant glucose infusion. The model includes state variables for plasma insulin, for insulin in the interstitial fluid and for the amount of glucose in the glucose space. Sturis found that the sustained oscillations could be attributed to the feedback between glucose and insulin. The dynamics were found to be heavily influenced by a 30-45 minute time delay for the effect of insulin on glucose production and a sluggish effect of insulin on glucose utilization.

Smith (1996) uses Stella to simulate the process of bone remodeling in which the surface of adult bone is constantly renewed. The model simulates the "journey" of bone remodeling with separate stocks assigned to resorption, reversal, and formation. The model may be used to shed light on the imbalance of bone resorption and formation that is often manifested by a pathological state such as osteoporosis. The model is documented in a unique manner in Smith's (1996) MS thesis to serve as a tool for medical education.

James Hargrove includes a "Stochastic Model of Bone Remodeling and Osteoporosis" in his 1998 book on Dynamic Modeling in the Health Sciences. Other chapters are devoted to a variety of topics including human cholesterol, circadian rhythms and tumor progression. (Also, his chapter on genotypes and phenotypes is useful reading if you plan to work on the industrial melanism exercises on the BWeb.)

Tarek Abdel-Hamid has used system dynamics models to examine human energy regulation and the implications for treatment of obesity. His 2002 paper in the System Dynamics Review is written for the modeling community. His 2009 book on Thinking in Circles about Obesity is written for a general audience.

Ozge Karanfil has done extensive work with system dynamics simulation to guide management of disorders of body water metabolism. The initial results are presented in her master’s thesis from Bogazici University (Karanfil 2005). A more recent paper appears in a special issue of Operations Research on the applications of operations research to health care (Karanfil and Barlas 2008). The OR paper describes A Dynamic Simulator for the Management of Disorders of the Body Water Homeostasis. The model simulates the body water control mechanisms under both normal and abnormal conditions, with a particular focus on intoxication/hyponatremia, the most common body fluid disorder. The simulator can be used to test various pharmacological interventions, including the use of hypertonic saline in delicate balance with drugs to increase urine flow.

Andrew Ford, Nov 2012 BWeb for Modeling the Environment
An Illustrative Example -- Riggs' Model of Shivering

These exercises show how a physiological model might be constructed in a step by step manner. The demonstration draws upon Douglas Riggs’ model of the regulation of body temperature. The model is documented (pages 383-400) in his 1970 text on Control Theory and Physiological Feedback Mechanisms. Riggs' documentation takes the form of equations, parameter values, feedback loops, electric circuit diagrams and equilibrium conditions. He concentrated on the equilibrium conditions because his purpose was to find the range of homeostatic control. He concluded that the physiological mechanisms (in the model) could control the body's core temperature at 37 °C (98.6 °F) over a range of ambient temperatures from approximately 5 to 45 °C. At the cold end of the range, control is achieved through shivering. At the high end, control is achieved through a combination of cutaneous vasodilatation and sweating. The system dynamics model may be verified by comparison with Riggs' original model. For example, the model may be used to check Riggs' assertions about the range of homeostatic control. By the end of the demonstration, you will see that we will accomplish more than simply duplicating Riggs' original model. The system dynamics model will show the "time dimension" which is missing from his work. The dynamic variations in body temperatures will appear automatically as the model is simulated on the computer.

Building the 1st Model

Riggs assumes that the body consists of two heat capacitances -- a relatively large central core surrounded by a relatively small amount of skin. The term "capacitance" comes from electric circuits where a capacitor is used to store energy. Riggs relies on electric circuit diagrams to show the structure of his model, but this approach is not needed with system dynamics. Rather, we'll use the "language of stocks and flows" to describe the underlying structure.

Figure 1 shows one stock to keep track of the energy stored in the core and a second stock for the energy stored in the skin. The stocks are measured in kcal (kilocalories). Time is measured in hours, and each of the flows is measured in kcal/hr. Temperatures are in °Celsius. Figure 1 shows the simple model along with the initial conditions. The core temperature is 37 °; the skin temperature is 31.57 °; and the ambient temperature is 27.5 °.

Figure 1 shows 2,146 kcal of energy stored in the core. Riggs defines a core thermal capacitance of 58 kcal/degree. Using this constant conversion factor, the initial core temperature would be 37 °C which translates to 98.6 °F. Energy in the core is increased by basal heat production and exercise heat production:

- Basal heat production is assumed to be 70 kcal/hr as long as the core temperature is 37 ° or less. If the core temperature should rise above 37 °, the basal heat production will increase in a linear fashion.

- Exercise heat production is assumed to remain constant at 22 kcal/hr regardless of the body temperature or the skin temperature
Energy in the core is reduced by two flows. The first flow is treated as a constant. The second flow is more complicated:

- Lung heat loss remains constant at 6 kcal/hr regardless of the body temperature or the ambient temperature.

- Heat transfer to the skin is controlled by several mechanisms involving heat transfer with minimal blood flow which remains during maximal coetaneous vasoconstriction and heat transfer by supraminimal flow. Riggs also describes a heat exchange mechanism involving counter-current heat exchange between arteries and veins. Riggs relies on the simplifying assumption that heat transfer is proportional to the temperature gradient between the core and the skin. Figure 1 shows the core gradient at 5.43 º at the start of the simulation. With this gradient, the heat transfer is 88 kcal/hr based on Riggs' assumption that there is a "resistance" to heat transfer to the skin which can be represented by a core to skin resistance of .0617 º per kcal/hr. The meaning of "resistance" may be clarified if you take the reciprocal -- its value would be 16.212 kcal/hr of heat flow for every degree of temperature gradient.

Figure 1. Initial Conditions for a simplified version of Riggs' model of body temperature control.
The lower portion of Figure 1 shows that energy stored in the skin is increased by the heat transfer and reduced by insensible perspiration and radiation. Heat loss from insensible perspiration is constant at 6 kcal/hr regardless of the skin temperature or the ambient temperature. Heat loss from radiation is proportional to the skin temperature gradient. Riggs assumes a skin to air resistance of 0.05 °C per kcal/hr. Taking the reciprocal gives a flow of 20 kcal/hr for each 1 degree of gradient. In Figure 1, the skin gradient is 4.07 °C, so the heat loss is around 4 times larger than the 20 kcal/hr.

**Testing the 1st Model**

Figure 1 uses the equilibrium diagram format, but a close inspection of the flows will reveal that the system is not exactly in equilibrium at the start of the simulation. The energy stored in both the core and the skin is declining at a very slow rate. But given time, the model might make the necessary adjustments and "find" a stable equilibrium condition (if it exists). To test if this will happen; the model is simulated over a 12 hour period with the ambient temperature held constant at 27.5 °C. Then the temperature is lowered 5 °C to simulate the model's response to colder conditions. Figure 2 shows the results.

![Figure 2. Simulation results from a "cold step test" of the first model.](image)

The first 12 hours of simulated behavior in Figure 2 show both the core temperature and skin temperature approximately constant, but the body is slowly losing energy. By the 12th hour, the core temperature is down to 36.86 °C (98.35 °F). The ambient temperature drops 5 °C in the 12th hour to test the responsiveness of the model. A 5 degree drop places the new ambient temperature well within the range of control expected by Riggs, but the model responds with a gradual decline in both the core temperature and the skin temperature. The new equilibrium is reached after around 24 hours. The approach to the new equilibrium may seem unusually slow, but Riggs does not include a "time dimension" that would allow us to compare results. (Milsum (1966, p. 77), on the other hand, gives examples of slow responses to "cold step" tests. But his text does not include a model.)
Feedback in the First Model

Clearly, the first model does not contain the control mechanisms needed to maintain the core temperature close to 37 °C. You might be tempted to conclude that the model lacks negative feedback which is essential for controllability. But this is not the case. Figure 3 shows four loops in the model. The positive loop involving basal heat production is not active because the core temperature never climbs above 37 °C. The three negative loops are active, but their actions do not provide the system with homeostatic control.

Figure 3. Feedback loops in the first model of body temperature control.
The 2nd Model Includes Shivering

Riggs' model includes the physiological responses of sweating when it's hot and shivering when it's cold. Shivering is the key to his model's homeostatic properties with cold conditions. (Shivering is an involuntary contraction of the muscles to release chemical energy into the core.) The next step is to incorporate Riggs' assumptions on shivering, as shown in Figure 4.

![Flow diagram for the second model of body temperature control.](image)

This diagram shows a new heat flow from shivering to increase the energy in the core. Shivering heat production is the product of a standard amount of heat from shivering and two multiplicative factors used to replicate Riggs' approach. Riggs assumes that the standard heat from shivering is 252 kcal/hr. This large value reveals the potential for shivering to counteract the heat losses seen in the previous model. In Figure 1, for example, skin heat loss from radiation is over 80 kcal/hr. If the skin temperature
gradient were to double due to a drop in ambient temperature, we would see an immediate increase of 80 kcal/hr of heat loss from radiation. If the "multiplicative factors" shown in Figure 4 were to call on 32% of the 252 kcal/hr of standard shivering, shivering would completely counter the extra 80 kcal/hr of heat loss.

The first of the two "multiplicative factors" in Figure 4 is the shivering initiation multiplier from cooler core. Figure 5 shows the shape of this multiplier. Notice that the multiplier is zero if the core temperature is 37 °C or higher. In other words, there is no shivering unless the core temperature falls below 37 °C. If this happens, the multiplier climbs rather quickly to 1.0 "turning on" the full power of the 252 kcal/hour of shivering. The nonlinear shape in Figure 5 matches Riggs' equation 11.E. Riggs specified this equation to match the empirical results by Benzinger (1963).

The second factor is the shivering multiplier from normalized temperature difference. The "normalization" depends on a normalizing factor, K, which depends on the core temperature as shown in Figure 6 below. This chart shows a linear growth in the normalization factor as the core temperature falls below 37 °C. If the core were at 35 °C, for example, the normalization factor would be at 25 °C.

The factor in Figure 6 is then used to normalize (i.e. reduce) the value of the skin temperature difference. A graph function (~) is used to represent the shape in Figure 6, but the final entry in the graph is set to 1 (rather than 0) to avoid division by zero. Riggs' normalized difference is based on a
critical skin temperature for extra shivering of 21 °. The calculation of the normalized difference is best illustrated with an example. Suppose the core temperature were 35 °, and the skin temperature were 11 °. With such a cold core, the first multiplier would "turn on" 100% of the standard shivering. The second multiplier calls on "extra shivering" if the skin temperature falls below the critical skin temperature of 21 °. In this example, the skin temperature is a full 10 ° below the critical value for extra shivering. Riggs normalizes this 10 degree difference by dividing by K, the normalizing factor shown in Figure 5. With a core temperature of 35 °, K would be 25, and the normalized skin temperature difference would be a negative 10/25 or -0.4.

The normalized difference is then used in Figure 7 to find the second of the two shivering multipliers. For this example, the second multiplier would be at 2.0. Since the first multiplier is at 1.0, the total heat production from shivering is twice the standard value of 252 kcal/hr. The graph in Figure 7 was selected to match Riggs' equation 10.E. This equation was designed to match the empirical work by Benzinger (1963).

![Figure 7. The shivering multiplier from normalized temperature difference as a function of the normalized temperature difference.](image)

New Feedback Loops from Shivering

Three additional feedback loops in the expanded model are shown in Figure 8. Each of these loops may be connected to Riggs's qualitative description of shivering. The negative loop at the top of the diagram involves the shivering multiplier from a cooler core. It will be active whenever the core temperature falls below 37 °. This is probably the loop that Riggs has in mind when he talks about "core modulated shivering."

A positive feedback loop appears in the middle of the diagram. It reveals a vicious circle that can lead the system to break down if the core temperature should fall too low. This loop is probably responsible for Riggs' finding that the "regulatory mechanisms must fail at very low ambient temperatures."
The third loop in Figure 8 is a negative loop at the bottom of the diagram. It involves the skin temperature, and is active when the skin temperature falls below the critical value of 21 °C. This loop is probably what Riggs has in mind when he refers to "skin-modulated shivering."

![Figure 8. New loops introduced by the addition of shivering.](image)

**Testing the 2nd Model**

The results of a "cold step" test with a 5 degree drop in ambient temperature are shown in Figure 9. The temperature drop occurs in the 12th hour of the simulation. The test shows that skin temperature would decline over the next two or three hours. The model exhibits a slight decline in the core temperature in the 12th hour, but the decline is not discernable in Figure 9. Nevertheless, this small decline triggers the shivering. Shivering increasing to around 45 kcal/hour. The increase is caused by the first of the two multiplicative factor (the shivering initiation multiplier from cooler core).

This cold step test confirms that the body would be able to maintain homeostatic control in the face of a five degree drop in ambient temperature. This result was expected from Rigg's description of the span of control. The test reveals that shivering would increase over a two to three hour period before reaching a steady state. If the body were permanently exposed to the 5 degree challenge, it would call upon 18% of the "standard amount of shivering." This test indicates that the shivering is triggered by the multiplicative factor involving small changes in core temperature. This response agrees with Riggs use of the term "core modulated shivering."
At this point, you are probably wondering if the dynamic response in Figure 9 matches Rigg's description of shivering. For example, you might be curious if Rigg's calculations show that the body requires 2-3 hours to attain the new equilibrium. You should know that the transient response cannot be confirmed or contradicted by Rigg's calculations. Riggs' analysis allowed him to derive steady state conditions, but it says nothing about the transient response. To confirm or reject the transient response in Figure 9, one might turn to Milsum (1966, p. 77) for examples of physiological responses to "cold step" tests.
Introductory Exercises with the Shivering Model

Six exercises are provided for students with an introductory interest in physiology. These exercises may be completed from the information on the website and in *Modeling the Environment*.

1. Build and Verify: Build the second model and verify that it performs as indicated in Figure 9. The model equations are listed in Table 1 below.

```
energy_in_core(t) = energy_in_core(t - dt) + (basal_heat_production + exercise_heat_production + shivering_heat_production - lung_heat_loss - eat_transfer) * dt
INIT energy_in_core = 2146
basal_heat_production = GRAPH(core_temp)
(37.0, 70.0), (38.0, 77.0), (39.0, 84.0), (40.0, 91.0), (41.0, 98.0), (42.0, 105)
exercise_heat_production = 22
shivering_heat_production = std_heat_from_shivering*first_factor*second_factor
lung_heat_loss = 6
heat_transfer = core_gradient/core_to_skin_resistance
energy_in_skin(t) = energy_in_skin(t - dt) + (heat_transfer - heat_loss_from_insensible_perspiration - skin_heat_loss_from_radiation) * dt
INIT energy_in_skin = 1831
heat_transfer = core_gradient/core_to_skin_resistance
heat_loss_from_insensible_perspiration = 6
skin_heat_loss_from_radiation = skin_gradient/skin_to_air_resistance
ambient_temp = if (time <12) then start_temp else start_temp-temp_drop
Ambient_Temp_in_F = 32+1.8*ambient_temp
Body_Temp_in_F = 32+core_temp*1.8
core_capcitance = 58
core_gradient = core_temp-skin_temp
core_temp = energy_in_core/core_capcitance
core_to_skin_resistance = .0617
critical_skin_temp_for_extra_shivering = 21
first_factor = shivering_initiation_mult_from_cooler_core
normalized_skin_temp_difference = skin_temp_difference/normalizing_factor_K
second_factor = shivering_mult_from_normalized_temp_diff
skin_capcitance = 58
skin_gradient = skin_temp-ambient_temp
skin_temp = energy_in_skin/skin_capcitance
skin_temp_difference = max(0,critical_skin_temp_for_extra_shivering-skin_temp)
Skin_Temp_in_F = 32+1.8*skin_temp
skin_to_air_resistance = .05
start_temp = 27.5
std_heat_from_shivering = 252
temp_drop = 5
normalizing_factor_K = GRAPH(core_temp)
(33.0, 47.0), (33.5, 42.0), (34.0, 36.0), (34.5, 31.0), (35.0, 25.0), (35.6, 19.0),
(36.0, 14.0), (36.5, 8.00), (37.0, 1.00)
shivering_initiation_mult_from_cooler_core = GRAPH(core_temp)
(34.8, 1.00), (35.0, 0.99), (35.2, 0.98), (35.5, 0.97), (35.8, 0.95), (36.0, 0.91),
(36.2, 0.83), (36.5, 0.69), (36.8, 0.45), (37.0, 0.00)
shivering_mult_from_normalized_temp_diff = GRAPH(normalized_skin_temp_difference)
(-1.00, 4.00), (-0.8, 3.20), (-0.6, 2.60), (-0.4, 2.00), (-0.2, 1.40), (0, 1.00)
```

Table 1. Equations for the 2nd model of body temperature control.
2. Find the "Span of Control" Under Cold Conditions

Repeat the cold step tests with larger and larger values of the temperature drop. Does the model show homeostatic control of the core temperature with ambient temperatures as low as 5 °? Does the homeostatic control fail with ambient temperatures below 5 °?

3. Width of the "Span of Control"

One of the input parameters in Riggs' model is the "std heat from shivering." He recommends a value of 252 kcal/hr. Suppose the uncertainty on this input is plus-or-minus 20%. How does the uncertainty in this single parameter change your estimate of the span of control from the previous exercise?

4. Experiment with a Hot Step Test

Rerun the model with a 5 degree increase in the ambient temperature in the 12th month of the simulation. Does the model provide homeostatic control under hot conditions?

5. What if There is a Delay in the Core Temperature-Shivering Loop?

The second model assumes that shivering will commence immediately whenever the core temperature falls below 37 °C. Figure 9 shows that the body would find the new equilibrium without any oscillations, and shivering would remain constant over time.

But you know from chapter 18 that a lag in the actions of a control loop might lead to oscillatory behavior. Consider the feedback control that acts through the core temperature and the onset of shivering. There might be a lag in the measurement of body temperature by the hypothalamus or a lag in the transmission of the measured temperature to the muscles via the spinal chord. Or perhaps there is a lag in how the muscles feel the temperature signal and begin to shiver. This exercise tests whether the introduction of such a lag could lead to oscillations in the simulated heat production from shivering.¹

Define a new variable called the lagged core temperature as shown in Figure 10. Use Stella's SMTH3 function with the core temp as the input to be smoothed. Set the lag time to 0.5 hours and assume that the lagged core temperature triggers the shivering initiation mult from cooler core. Set DT to 1/16th of an hour to ensure numerical accuracy. Then simulate the new model to verify the results shown in Figure 11 below.

¹ I am now aware of any studies or papers that describe shivering in this meaner. So this exercise is a "what-if experiment" to see how the model responds. Meanwhile, students of physiology might be interested in Milsum’s (1966, p. 76) description of work by Benzinger (1963) in which "sudden changes in skin temperature, either up or down, produced transient overshoots in the metabolic heat rates before these settled down to suitable new steady states."
6. Which Loops Act with a Lag?
Use the // convention to revise the causal loop diagram in Figure 10 to represent the time lag in the previous exercise. How many feedback loops operate with a lag in the new model?
Advanced Exercises with the Shivering Model

Three exercises are provided for students interested in advanced study of physiology. You will need to take advantage of your previous study of physiology and you will need a copy of Rigg's (1970) *Control Theory and Physiological Feedback Mechanisms*.

7. Add Sweating to the Model

Expand the model to incorporate Riggs' description of sweating. Test the model under hot conditions to learn if the sweating mechanisms are sufficient to achieve homeostatic control of core temperature up to ambient temperatures of 45 °.

8. Add Coetaneous Vasodilatation to the Model

Expand the model to incorporate Riggs' description of coetaneous vasodilatation. Test the model under hot conditions to learn the range of homeostatic control.

9. Discussion Questions

Review Riggs' description of the model on pages 384-400 and reflect on the ways in which his approach differs from the system dynamics simulations shown here. Then answer any of the following questions:

1. Why do you think Riggs confines his attention to the equilibrium conditions?
2. Do you think Riggs could use his model to show behavior over time?
3. Do his loop diagrams follow the conventions explained in *Modeling the Environment*?
4. Do his "electrical" diagrams follow the conventions in *Modeling the Environment*?
5. Did you find his loop diagrams and his "electrical" diagrams effective in helping you to appreciate the underlying structure of his model?
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End Note

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1 A capacitor is a storage device in electrical circuits, and Riggs uses term “capacitance” for energy storage in the body. This terminology makes sense given Rigg's background in both control engineering and physiology.