

# Rudimentary Model of Glucose Response to Stress

Nasha Rios-Guzman  
*University of South Florida*

Advisors:

Arcadii Grinshpan, Mathematics and Statistics

Andrew Henry, Endocrinology, Diabetes and Metabolism; Brandon Regional Hospital and Tampa  
Community Hospital

Problem Suggested By: Nasha Rios-Guzman

**Abstract.** A simplistic multifactorial model was crafted to represent change in plasma glucose concentrations after increases in stress hormones above baseline. A sample application of the predictive use of this model was demonstrated, and a reflection on possible models in diabetic populations was described. The potential for use of this model in conjunction with current models is discussed, as well as the issues pertinent to such a basic model.

**Keywords.** plasma blood glucose, stress hormones, multivariate models

Follow this and additional works at: <http://scholarcommons.usf.edu/ujmm>

 Part of the [Mathematics Commons](#)

UJMM is an open access journal, free to authors and readers, and relies on your support:

[Donate Now](#)

---

## Recommended Citation

Rios-Guzman, Nasha (2017) "Rudimentary Model of Glucose Response to Stress," *Undergraduate Journal of Mathematical Modeling: One + Two*: Vol. 8: Iss. 1, Article 6.

DOI: <http://doi.org/10.5038/2326-3652.8.1.4887>

Available at: <http://scholarcommons.usf.edu/ujmm/vol8/iss1/6>

---

# Rudimentary Model of Glucose Response to Stress

**Creative Commons License**



This work is licensed under a [Creative Commons Attribution-Noncommercial-Share Alike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/).

## PROBLEM STATEMENT

Many mathematical models for diabetes exist, including complex arrays of variables that affect plasma blood glucose. While there is a clear understanding that stress hormones increase blood glucose, the author is not aware of mathematical models specifically delineating the mechanism for stress hormones to increase plasma blood glucose. This problem can be addressed through a basic multifactorial model, which can potentially be applied by those at risk for hyperglycemia in the face of stressful events or as a result of particular medications.

## MOTIVATION

Stress of any form affects the human body in a multitude of ways, one of which being that it prompts the release of hormones which support the body in handling difficult situations. Those with certain health conditions, such as diabetics, must pay special attention to the way that stress may impact their health. Stress hormones including cortisol, epinephrine, and norepinephrine all—among other things—act to increase the amount of plasma glucose ready for use during urgent situations (Marcovecchio and Chiarelli, 2009). Even glucagon is considered a stress hormone that works to that end, outside of its role as a remedy for hypoglycemia (Jones, Tan, and Bloom, 2012).

The human body has complex metabolic pathways for the digestion, storage, and use of glucose, which are critical for any individual to have enough energy to carry out many other processes, seeing that glucose is the most direct fuel that the body can use (Smith et al., 2009). Once glucose is introduced in the blood stream from the digestive system, it will reach a variety of destinations. Tissues in the body which require insulin to process glucose become problematic for diabetics, since the main feature of diabetes is elevated blood glucose levels, hyperglycemia, from improper transport of glucose from the bloodstream into cells. This generally takes the form of an inability to produce insulin, type 1 diabetes, or an otherwise impaired utilization of insulin, type 2 diabetes (Hernandez, 2016).

In a nondiabetic, glucose travels in and out of tissues according to a negative feedback mechanism involving insulin, so that an ideal level of free-floating plasma glucose is sustained and available for use (Zullo, 2009). However, when the body experiences stress, the sympathetic nervous system is activated to deal with emergencies by a “fight or flight” mechanism, and part of this activation involves the secretion of stress hormones which stimulate a higher rate of glucose release into the blood (The Science of Stress). Similarly, it is known that taking medicines related to stress hormones, such as glucocorticoids, can increase diabetes risk by altering the individuals’ usual glucose levels (Hwang and Weiss, 2014).

There are a plethora of models describing the ins and outs of glucose with regards to insulin secretion, insulin sensitivity, glucose absorption, glucose secretion, physical activity, and so on, but the author is not aware of a model describing the way stress hormones also affect blood sugar. Although plenty of research on the subject exists, and although its principles may seem relatively simple, it may be helpful to construct a basic mathematical model also including the mechanism of these hormones to affect blood glucose. Writing a multivariate function for this feature of glucose metabolism could help establish a basic reference of how changes in stress levels or the intake of certain medications may alter future glucose levels in an individual.

## MATHEMATICAL DESCRIPTION AND SOLUTION APPROACH

### *A Simplistic Multivariate Model of Change in Plasma Glucose by Stress Hormones*

Based on information from “Role of Counterregulatory Hormones in the Catabolic Response to Stress” by Gelfand et al., 1984, I proposed a simple mathematical model of how four stress hormones affect plasma blood glucose:

$$G(c, \alpha, e, n) = G_{baseline} \left[ 1 + \frac{0.2c}{6 \text{ mg}(m^{-2}h^{-1})} + \frac{p_1\alpha}{4 \text{ ng}(kg^{-1}min^{-1})} + \frac{p_2e}{0.6 \text{ }\mu\text{g}(m^{-2}min^{-1})} + \frac{p_3n}{0.8 \text{ }\mu\text{g}(m^{-2}min^{-1})} \right] \quad (1)$$

In function (1), the variables represent stress hormones present above normal levels, where “c” is cortisol, in  $\text{mg}(m^{-2}h^{-1})$ , “ $\alpha$ ” is glucagon, in  $\text{ng}(kg^{-1}min^{-1})$ , “e” is epinephrine, in  $\mu\text{g}(m^{-2}min^{-1})$ , and “n” is norepinephrine, in  $\mu\text{g}(m^{-2}min^{-1})$ . Each variable is divided by its units in values mirroring the infusion rates stated in the Gelfand et al. article. This serves to normalize each variable, so that what is being shown from each component is not the actual rate of infusion, but a standard unit describing how much of each hormone is present above baseline levels. Ignoring the coefficient in the numerators, the variables will cancel to a value of 1 in the case of severe stress which constitutes the levels of each variable shown in the denominators. Likewise, units of these variables cancel with their denominators in the function. Plasma glucose, “G” may be reported in either  $\text{mg}/\text{dL}$  or  $\text{mmol}/\text{L}$ , and “ $G_{baseline}$ ” is a constant that represents an individual’s normal level of plasma glucose in the absence of abnormal stress.

Each hormone is given a coefficient based on the proportion it could contribute to a rise in blood sugar after secretion. In the Gelfand et al. study, the only hormone whose effect on glucose was measured on its own was cortisol, which raised plasma glucose from 20% to 25% after being infused at the rate shown in the denominator of its part of the function. The average rise in glucose due to all hormones being infused together was reported between 60% and 80%. Since it is not clear what percentage glucagon, epinephrine, or norepinephrine raised blood glucose individually within this, they were initially given placeholders of “ $p_1$ ”, “ $p_2$ ”, and “ $p_3$ ” respectively. Focus was placed on the minimum possible value of a 60% overall rise in plasma glucose and after cortisol was given a coefficient of 0.2 for 20%, the remaining 40% was evenly distributed among the other hormones:

$$G(c, \alpha, e, n) = G_{baseline} \left[ 1 + \frac{0.2c}{6 \text{ mg}(m^{-2}h^{-1})} + \frac{0.133\alpha}{4 \text{ ng}(kg^{-1}min^{-1})} + \frac{0.133e}{0.6 \text{ }\mu\text{g}(m^{-2}min^{-1})} + \frac{0.133n}{0.8 \text{ }\mu\text{g}(m^{-2}min^{-1})} \right] \geq 0 \quad (2)$$

Function (2) must be either zero or positive since all variables, including  $G_{baseline}$  describe some concentration of chemical, and it is not possible for such concentrations to be negative in the real world.

### *Application of the Model*

Since this model assumes a constant baseline glucose, it is only practically applicable for nondiabetic individuals. If such an individual normally has a steady glucose level of 80 mg/dL and is to start a medication regimen that increases his or her circulating cortisol levels to half of the standardized rate, 3 mg(m<sup>-2</sup>h<sup>-1</sup>), leaving other hormones unaffected, the following would be shown:

$$G = 80 \frac{mg}{dL} \left[ 1 + \frac{0.2(3mg(m^{-2}h^{-1}))}{6 mg(m^{-2}h^{-1})} + \frac{0.133(0)}{4 ng(kg^{-1}min^{-1})} + \frac{0.133(0)}{0.6 \mu g(m^{-2}min^{-1})} + \frac{0.133(0)}{0.8 \mu g(m^{-2}min^{-1})} \right] \quad (3)$$

It is assumed there are no increases in glucagon, epinephrine, or norepinephrine above baseline levels, so that  $\alpha$ ,  $e$ , and  $n$  are 0. Completing the calculations in (3) results in (4):

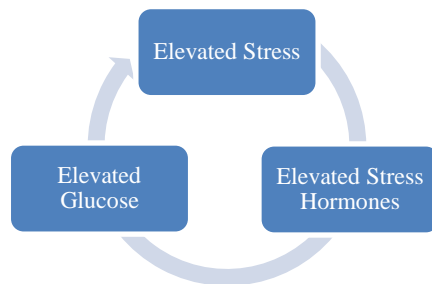
$$G = 80 \frac{mg}{dL} [1 + 0.2(0.5)] = 80 \frac{mg}{dL} [1.1] = 88 \frac{mg}{dL} . \quad (4)$$

Where, predictably, only half the amount of cortisol present in severe stress is circulated, so that the blood glucose is raised 10% from baseline, rather than 20%.

### *In the Case of Diabetics*

Diabetics particularly type 1 diabetics, lack the negative feedback mechanism which keeps a nondiabetic's plasma glucose relatively constant. This mechanism also helps to cap off increases in stress hormones to only what is necessary, since these are the hormones responsible for raising blood glucose as needed.

In a case where a diabetic lacks delivery of any exogenous insulin, one could theorize that rises in stress hormones would trigger a catastrophic positive feedback mechanism. In such a loop, stress would feed into stress hormones, which would feed into elevated glucose levels, which would feed back into stress:



**Figure 1.** Diagram representing the positive feedback loop in uncontrolled type 1 diabetes.

As glucose is not being fed into cells, extra solute in the blood increases risk for dehydration, among other issues. Additionally, the fact that practically no fuel is being delivered to deal with the initial stressor leads to more production of hormones to continue to try to remedy the issue. This increases the concentration of blood glucose to unhealthy levels and only makes the condition worse.

Such a positive feedback mechanism could be represented by the logistic growth equation, in which levels of these components will rise through time until they reach a threshold where continued growth is no longer feasible. However, experimentally gathering data on an upper limit to glucose levels in the absence of insulin would be difficult since such an endeavor would

be incredibly risky to participants, and thus unethical. Perhaps in the future, studies on small rises in blood sugar, sans insulin, over extremely short periods of time could potentially be used to create models of the feedback loop without much risk to participants.

## DISCUSSION

### *A Simplistic Multivariate Model of Change in Plasma Glucose by Stress Hormones*

While the model (1) presented here seems rather straightforward, some notes should be made about the research data used to construct this mathematical model. In addition to the Gelfand et al. study, experiments need to be carried out to ascertain what proportions of a total rise in glucose are accounted for by the stress hormones discussed—namely glucagon, epinephrine, and norepinephrine. For some reason, singular attention was paid to cortisol's responsibility in affecting glucose. Consequently, only cortisol's role in the function is accurate to the data. An assumption of the other hormones' equal contribution to changes in plasma glucose may be completely false. Perhaps one of the three hormones mentioned plays an even larger role than cortisol, affecting glucose up to 40%, while the others contribute scantily. There is no way to know that relationship between these variables without more distinct experimental data.

Furthermore, the Gelfand et al. study only used a small number of obese subjects, primarily female (1984, p. 2239). Such a limited population sample means that the study, and thus this model based on its data, may lack external validity. Another worry is that the study is quite old. Over 3 decades have passed since its publication, and more current knowledge of the matter at hand should be sought out.

### *Application of the Model*

Such a direct model allowing us to calculate glucose concentrations in response to stress hormones may be an oversimplification of the physiology at work. The relationship between elevating stress hormones and resulting plasma glucose levels may not be as obvious as it may seem. Once again, there is a need for more experimental data and an evaluation of existing research on the mechanism by which hormones such as cortisol navigate the body, and whether other chemicals may interfere with cortisol's role in elevating blood glucose.

Even with potential issues, components of this model should be implemented into existing models of the insulin-glucose feedback system. In 2000, Tolić, Mosekilde, and Sturis, presented their comprehensive models of the insulin-glucose system using differential equations, with the following equation representing the rate of change in plasma/intercellular glucose at any one time:

$$\frac{dG}{dt} = G_{in} - f_2(G) - f_3(G)f_4(I_i) + f_5(x_3) . \quad (5)$$

In (5), the “ $f$ ” values are appended functions which mediate different aspects of glucose uptake and secretion. Of particular interest is the last one:

$$f_5(x_3) = \frac{R_g}{1 + e^{a\left(\frac{x_3}{Vp - C_5}\right)}}. \quad (6)$$

Function (6) represents hepatic (liver) production of glucose considering opposing effects from one of the insulin delay variables in the model (Tolić et al., 2000, pp. 363-364). Note that the “a” is changed from the original “ $\alpha$ ” in the Tolić et al. text, in order to avoid confusion with the different variable established earlier. The simple model presented in this paper represents that extra glucose released into plasma—including from the liver—is stimulated by stress hormones. The parameters given by the researchers for the above function appear to show that all values present are constants except for “ $f_5$ ” (hepatic production) and “ $x_3$ ”, representing an effect of insulin delay (Tolić et al., 2000, p. 363). Certainly there must be a way to attach the linear, multifactorial model of stress hormones onto this to better represent hepatic production, which is controlled by more than just insulin delays.

### *In the Case of Diabetics*

Diabetes, being a problem of elevated and variable blood sugar concentrations, does not fit with the model presented here, which depends on a constant baseline glucose level as part of the function. Additionally, stress models involving diabetics are expected to have issues with accuracy over the long run. The longer an individual has diabetes, the more deteriorated their stress hormone response becomes (Dr. Andrew D. Henry, 2016). This means that over time, diabetics will not fit into given models as well, and so cannot refer to them reliably.

The positive feedback loop discussed as the natural trend of type 1 diabetics lacking insulin is an interesting point for future study. Possible applications of such a model would be to give a more defined idea of what happens in completely uncontrolled diabetes, what the timeline for acute hyperglycemic emergencies might be, and to shed light on the implications of stress to create persistent hyperglycemia when not properly addressed in a treatment regimen. Once again, designing studies to effectively determine the mechanism without hurting participants is a priority. Surpassing risks, however, is some potential benefit to understanding appropriate models that fit nondiabetics more realistically.

## CONCLUSION AND RECOMMENDATIONS

Using data from a 1984 study by Gelfand et al., a rudimentary multivariate model was crafted to represent change in plasma glucose concentrations in response to increases in stress hormones above baseline. The model successfully allowed for the estimation of blood glucose levels after input of an artificial amount of excess cortisol. The model’s reliance on limited data, simplicity, and restriction to nondiabetics are issues. Nevertheless, the author is hopeful and recommends that a model like this be fused with current models to show how stress hormones play a significant role in glucose levels.

## NOMENCLATURE

Variable	Definition	Units
c	cortisol	mg(m <sup>-2</sup> h <sup>-1</sup> )
α	glucagon	ng(kg <sup>-1</sup> min <sup>-1</sup> )
e	epinephrine	μg(m <sup>-2</sup> min <sup>-1</sup> )
n	norepinephrine	μg(m <sup>-2</sup> min <sup>-1</sup> )
G	[plasma glucose] after stress	mg/dL or mmol/L
G <sub>baseline</sub>	[plasma glucose] before stress	mg/dL or mmol/L

## REFERENCES

- Dr. Andrew D. Henry, Interview, December 12<sup>th</sup>, 2016. Board Certified Endocrinologist.
- Gelfand, R. A., Matthews, D. E., Bier, D. M., and Sherwin, R. S. (1984) Role of counterregulatory hormones in the catabolic response to stress. *The Journal of clinical investigation*. U.S. National Library of Medicine.
- Hernandez, D. (2016) Type 1 vs. Type 2 diabetes: What's the difference? - Vital Record. *Vital Record*. Texas A&M University Health Science Center.
- Hwang, J. L., and Weiss, R. E. (2014, July 27) Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. *Diabetes/metabolism research and reviews*. U.S. National Library of Medicine.
- Jones, B. J., Tan, T., and Bloom, S. R. (2012) Minireview: Glucagon in Stress and Energy Homeostasis. *Endocrinology* 153, 1049–1054.
- Marcovecchio, M. L., and Chiarelli, F. (2012) The Effects of Acute and Chronic Stress on Diabetes Control. *Science Signaling* 5.
- Smith, J. M., Maas, J. A., Garnsworthy, P. C., Owen, M. R., Coombes, S., Pillay, T. S., Barrett, D. A., and Symonds, M. E. (2009) Mathematical Modeling of Glucose Homeostasis and Its Relationship With Energy Balance and Body Fat. *Obesity* 17, 632–639.
- The Science of Stress. *Weber State University*. Weber State University.
- Tolić, I. M., Mosekilde, E., and Sturis, J. (2000) Modeling the Insulin–Glucose Feedback System: The Significance of Pulsatile Insulin Secretion. *Journal of Theoretical Biology* 207, 361–375.



Zullo, A. The Role of Hormones in Homeostasis. *15.06.09: The Role of Hormones in Homeostasis*. Yale National Initiative.