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Additional comments on the bistable network model of brain ischemia

Donald J. DeGracia, Ph.D.*

Department of Physiology, Wayne State University, Detroit, MI 48201, U.S.A.

(In response to editorial comments)

Dr. Hossmann provides a lucid and concise summary and a sympathetic critique of the bistable model and its potential role in cerebral ischemia research. He rightly gets to the heart of the matter in recognizing that the bistable model as currently presented is inspired primarily by envisioning transient global ischemia. Such an insult is characteristic of commonly used laboratory models of global ischemia including cardiac arrest, bilateral carotid artery occlusion (with or without hypotension) or four vessel occlusion.

The other ischemic pathophysiologies Dr. Hossmann describes, primary ischemic cell death, and the gradual time-dependent increase in the threshold of energy failure are both characteristic of focal ischemia. The application of the bistable model to focal ischemia is touched on only briefly in the 4th paper of the series. While it was discussed there that focal ischemia will require a more complex type of network analysis, we offer brief additional comments here in relation to Dr. Hossmann's appropriate concern to disambiguate the pathophysiologies induced by the various experimental brain ischemia models.

A key to applying network analysis to any form of brain ischemia lies in the integral used to define the amount of ischemia, *I*. We can envision an infinity of curves of any degree of blood flow reduction for any duration, in any arbitrary volume of the brain, constrained only at the upper limit of the death of the organism. Probably any and all of these curves occur in human brain ischemia under some condition or another. The key question in relation to the bistable model becomes: is the concept of the post-ischemic state space (and implicitly, the underlying networks) relevant in general, or is it only applicable to the circumscribed case of transient complete global ischemia tackled in the current series of papers?

The ultimate intent of the approach behind the bistable model is to provide a systematic and unified framework for conceptualizing brain cell outcome after exposure to ischemia. Since it is a mathematical approach, we should expect some post-ischemic state space to follow from any blood flow reduction scenario. There can only be three possible cellular outcomes under any circumstance: survival, death during ischemia or death during reperfusion. The physical limits on any phenotype described by any arbitrary post-ischemic state space will be the viability thresholds that Dr. Hossmann has played such an instrumental role in defining.

Thus, the present set of papers should be seen as addressing only what is perhaps the simplest possible blood flow reduction scenario. The purpose of tackling the simplest case is to work towards building an empirically derived state space under the circumscribed conditions of various durations of transient complete global ischemia. Even this simplest case is complicated by the differential neuronal ischemic vulnerability and other issues as discussed in the series.

However, once an empirical state space can be derived on this basis, one can imagine expanding the program to determine the family of state spaces corresponding to the family of all arbitrary curves of blood flow reduction (within physiologically realistic limits). This of course would include any form of focal ischemia. In this fashion there would be a convergence between the wide variety of experimental models now in use and the general applicability of the post-ischemic state space concept. It is hoped that such a systematic framework, in which network analysis is only one amongst many tools brought to bear on the problem, will assist in alleviating the type of misconceptions to which Dr. Hossmann refers. Thus, as Dr. Hossmann acknowledges, the use of the term "towards" is appropriate at this early stage of the application of network concepts to the problem of brain ischemia and, as Dr. Hossmann also acknowledges, much work remains to be done.

Donald J. DeGracia, Ph.D.
Department of Physiology
Wayne State University
4116 Scott Hall, 540 East Canfield Ave.
Detroit, MI 48201, U.S.A.

* ***Correspondence should be sent to*:**
Donald J. DeGracia, Ph.D., Department of Physiology, Wayne State University, 4116 Scott Hall, 540 East Canfield Ave., Detroit, MI 48201, U.S.A. Phone 313-577-6745; Fax 313-577-5494; E-mail: ddegraci@med.wayne.edu