Neural computation in excitable media.

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Theoretical Neuroscience seeks to delineate conceptualizations which would generate explanatory and predictive accounts of empirical observations in the Neurosciences. At its inception in the late part of the 19th Century, it dealt creatively with what one could call 'virtual objects'. For instance Sherrington's Synapse and 'central excitatory/inhibitory states' were ideas whose actualization in real mechanisms required many years of experimental work. Similarly, ideas of 'wiring diagrams' of neural connectivity (24,11) and the role of neurons acting in assemblies rather than in isolation (30) were formulated as directives for empirical investigation. In the late 1940s, Theoretical Neuroscience took a decisive turn to become, essentially, the current Computational Neuroscience. Several signal events occurred at that time, in large measure associated with or triggered by the "Cybernetic Revolution'. For a short list of these influences I single out Turing machine computation and Shannon's information theory, merging to the idea of the brain as an information processing machine in which binary neural impulses would function as a code for external physical events : both ideas being sustained by the fertile ground of the then prevailing logical atomism in Epistemology, and of Cartesian representationalism. These ideas are epitomized in the influential work of McCulloch and Pitts (42) on '*the logical ideas immanent in nervous activity*' that established that computation on these principles can prove all theorems of the Principia Mathematica. The single neuron methodology of recording neural activity enabled experimental neurophysiologists to supply the data that the theory required, thus sustaining a circularity of seemingly mutual validation. Concurrently, computational models have sought to determine principles by which networks of neurons can process and represent information in digital form. Thus consolidated the ideology of the 'Digital Brain'.

The importance of this constellation of concepts lies in having created a vocabulary that has shaped the discourse in current theoretical neuroscience to the extent that it is for all practical purposes synonymous with computational neuroscience. The terms of this vocabulary, and the premises they entail, have undergone some evolution in meaning: for instance, some investigators limit information transmitted to 'mutual information' (i.e. essentially correlation) (12); others liberate 'computation' from confinement to Turing Machine principles to various other forms of input-output transformations of which, for instance, nonlinear dynamics and chaos is gaining momentum (23). Nonetheless, paraphrasing MacArthur: old ideas never die, although fading they continue to however subtly influence thought patterns. Hence my claim for "epistemic hygiene' in theoretical neuroscience, on which I have commented at another occasion (57a). I will in the following use the contentious terms 'computation and 'information' in their originary and basic every-day connotation: the first as any process that transforms an input to an output; the latter that -in accord with etymology- as imparting a new configuration on an entity, whatever its nature.

The seductive simplicity and clarity of the principles enunciated in the incipient stage of computational neuroscience have swept alternative considerations readily aside: many of them can be subsumed under the term 'mass action' ,

introduced by W. Freeman in 1970 (22). I include here also the neural simulation work in the Neurodynamics of Beurle (4), Wilson and Cowan (60) and others, concerned with the role of patterns of propagating waves generated by neuronal interactions in large assemblies.

Brain-Cell Microenvironment:
In a broad generalization, the conceptual neuron of computational neuroscience can be considered as encompassing two distinct, though interrelated, abstractions: one unit of abstractions is the neuron, the other the synapse. Some aspects of the rich dynamics of the latter is now well established: I refer to the changes of synaptic efficacy with repeated or persistent activity. Beyond this established fact, I single out two particularly suggestive possibilities whose implications still need to be delineated: one, that dendrites can function as filters of presynaptic activity, potentially enabling differential distribution of axonal activity to different recipient neurons (38, 39, 40); the other, the role of the perisynaptic and peridendritic space for chemical signaling via diffusion. On the basis of computational simulations, Egelman and Montague (17, 18, 58) proposed that activity induced peridendritic calcium fluctuations can act as a volume transmitted signal for regulating transmitter release, or modifying patterns of spike generation. Similarly, models of the diffusion kinetics of glutamate in extrasynaptic space show that exocytosis of single vesicles can sustain activation of high-affinity receptors in the immediate perisynaptic vicinity (49).

These recent computational models of extrasynaptic chemical effects on neural structures invite renewed attention to a vast array of experimental findings and models which implicate the extracellular microenvironment in neuronal activity. In 1956, Frankenhauser and Hodgkin (21) demonstrated that repetitive activity in the squid giant axon declines due to accumulation of potassium ions in the axon's surrounding environment. The topic of the 'Brain-Cell Microenvironment (a term introduced by Schmitt and Samson at a workshop of the Neuroscience Research Program in 1969) was intensively pursued by Kuffler and associates in studies of the leech nervous system: Kuffler and Nicholls (35) developed many fundamental ideas about interactions between neurons and glia to account for the role of diffusion of substances in intercellular clefts; amongst them the notion that the three-dimensional extension of extracellular space resembles the water phase of a foam (34). Primarily concerned with potassium and calcium signals in the 'Brain-cell Microenvironment, Nicholson (44) wrote in 1979: " *we must begin to see the electrical signals and their communication network as a fast control system for ionic and molecular fluxes .... What we are beginning to appreciate is that neurons are actually a form of biological cell and not merely a nonlinear electrical element"*. The dynamics of Potassium in this microenvironment was further elucidated by Gardner-Medwin (26). Recently, Rusakov and Kullmann (50) developed a quantitative framework for estimating the diffusion of molecules in size from Ca^{2+} ions to neurotrophins in brain extracellular space.

A second, largely independent, thread of investigations yielded a wealth of evidence for the electrical and chemical activity in astrocyte glia, with properties intersecting richly with those of the neurons with which they share the extracellular environment for interaction. Though not generally heeded, it is a reminder to neurophysiologist and computational neuroscientist: "don't forget the Glia". Dismukes (16) reviewed in 1979 the evidence for non-synaptic release of neuromodulators as basis for non-synaptic ('paracrine') communication among neurons: his lead article in BBS elicited virtually unanimous support, with one reviewer proposing some form of multimodal information processing in the Nervous System. Theoretical and experimental studies, reviewed in detail by Nicholson in 1995 (45), attributed to glia a spatial buffering mechanism for dispersing accumulating potassium ions. More recent anthologies assembled an abundance of data attesting to the the richness of metabolic and electrical phenomena displayed by astrocyte glia (33) with potential effects on the Brain-Cell Microenvironment (see also: 2, 3, 8, 10, 52, 54). Neuromodulator functions unrelated to synaptic transmission were also proposed (13,14,15). These and many other aspects of the rapidly accumulating evidence on neuron-glia interactions suggest to LoTurco (37) that the *"Neural Circuits of the 21st Century"* are being ushered in. In another context, Vizi & Labos (56)argued for some form of 'field effects' acting on neurons and synapses, comprising electrical and chemical processes of various kinds, and acting over some distances in neural tissue.

A new terminology seemed called for to differentiate intercellular communication through connecting structures (synapses, gap junctions) from diffusion-mediated chemical effects through extracellular space: the terms 'wiring transmission' and 'volume transmission' are to designate these two distinct communication phenomena in brain tissue (1). This duality of intercellular communication is also of considerable potential relevance for Neuropharmacology (66). The terminological distinction must not obscure the fact that both forms of transmission are concurrent and

reciprocally interacting via the brain-cell microenvironment as a communication channel. But the detailed nature of such interactions, and their functional significance are at this point far from clear, and open to speculation: for instance, the possibility that chemical signaling is involved in dynamically coordinating neuron assemblies to functional units has been suggested (43).

Diffusion of chemical substances in the brain cell microenvironment attracted recent interest in regard to liberation of Nitrous Oxide with neural activity: Husbands et al. (32, 46) and Gally et al (25) have shown an enhancing effect on learning in Neural Networks. Modeling chemical modulation of neural processes was investigated by Coolen et al (9): it appears that the modulation might serve as an additional degree of freedom for pattern recognition, or for choosing from among partially overlapping trajectories in state space.

Ion channel conductances:
The principal, though not always explicitly stated target of the presumed neuon-glia interactions are transmitter mechanisms at the synapse. In distinction, I concentrate here on ion conductances of neural membrane channels. I sought to obtain in computer simulations an intuitive sense for possible manifestations of such interactions in the Brain-Cell Microenvironment. Conductances seemed a plausible choice since experimental and simulation studies have identified an appreciable number of ion channels with distinct properties (31), and some of the factors that modify their control parameters. Harris-Warrick (29), McCormick (41), Butler et al (6), Butera et al (5) and Canavier (7) are among the investigators who demonstrated in computer models effects of neuromodulators and ion conductances, and Liu et al (36) described three sensors for intracellular Ca which affect ion channels at different time scales. There is also evidence for various forms of activity related effects on ion conductances (53), for state-dependent effects on conductances (27), and for their mutual interdependence, in a sense self-organizing themselves to a narrow range of acceptable parameter values (20). It is thus fairly certain that channel dynamics can be the target of a variety of contextual variables. The question is: can volume transmission in extracellular space be shown to be one of them ?

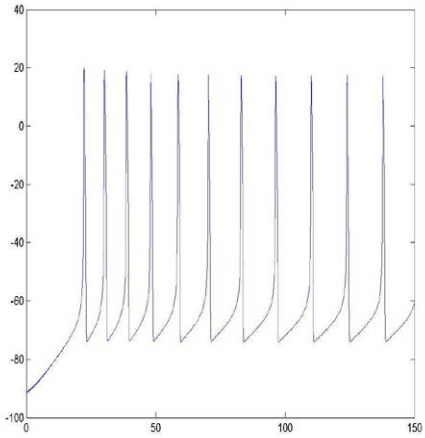
The Neuron Model
For making simulations computationally tractable, it becomes usually necessary to resort to a reduced neuron model in which realistic neuron performance is captured by fewer than the total complement of identified channels. I adopted the simplified model neuron and parameter values describe d by Wilson (61): the reduced model is based on four ion currents (I_{Na}, I_K ,I_T and I_{AHP}) . The equilibrium potential or Na, K and Ca are taken from the model of Rush and Rinzel (51). The model also includes provisions for synaptic interconnections, applying Rall's (48) *alpha* function.

I applied this neuron model to examine the following conjecture: extracellular Ca^{2+}concentration decreases rapidly and transiently during neural activity. Xiong et al (64) showed that this reduction excites and depolarizes hippocampal neurons by activating a nonselective cation channel. This activation is presumably associated with removal of surface charges from the neuron membrane. By this means, the availability of Ca^{2+} at or near the membrane surface affects the gating properties of ion channels (65). I, furthermore, assumed that the activity related reduction of Ca^{2+} in a neuron's immediate extracellular vicinity will establish a concentration gradient in the neuron's extracellular surround, withdrawing by diffusion Ca^{2+} ions from neighboring neurons' environment. If activated, they would, in turn, reduce extracellular Ca^{2+} in their respective neighborhoods, while previously active neurons will cease firing because of excessive intracellular Ca^{2+} accumulation. A waxing and waning pattern of diffusion gradients should be expected to pulsate in the extracellular field of nearby neurons. In the equation for the membrane voltage, the conductance for I_T increases linearly with the computed extracellular Ca^{2+} concentration. This translates in the membrane potential equation to protracted recovery after depolarization, and lowering of the threshold for subsequent stimuli, at some values also bursting. Hence, neighboring neurons in an assembly are expected to fire in a shifting pattern and to contribute to a complex sequence of superimposing waves of Ca^{2+} reduction in their extracellular space. Diffusion of Ca^{2+} was calculated by a discrete Laplace Transform of the diffusion equation (57). The question addressed in this simulation is, in a sense, the converse of that investigated by Falcke et al (19) : their studies explored the coupling of membrane currents to the intracellular dynamics of Ca^{2+} storage and release. (for a commentary on computational simulation and modeling, see footnote).

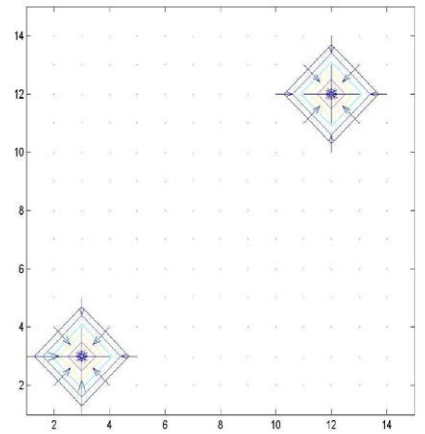
Simulation Results:

I tested this model under two conditions: one, in an assembly of neurons without synaptic connections; the other in an assembly with neurons connected by electrical junctions. The following figures illustrate simulation data obtained with the Matlab ode23 differential equation solver.

Figure 1 (below, left) : Discharge pattern of the model neuron with the initial parameters identical to those applied in all subsequent simulations.



For the first series of simulations, I situated 15x15 identical neuron models of the previously specified characteristics in an array, without any synaptic or electrical junctions. Two of these neurons were stimulated repetitively. Figure 2 , below, shows a gradient display of summed neural activity generated in 30 msec of simulation: as to be expected, the responses are localized to the sites of the stimulated neurons (2,3) and (12,12).



This activity pattern of the neuron matrix changes drastically when the assumptions of the hypothesis under test are applied. The effect of the activity related spread of the perineural Ca^{2+} reduction is that unstimulated neurons in the matrix start firing as they are reached by the wave of (postulated and simulated) Ca^{2+} reduction. Finally, the secondarily active neurons also initiate propagating waves of the assumed Ca^{2+} reduction. A complex panorama of neural activity and I_T conductance and correlated changes in perineural Ca^{2+} concentration develops within the first 5 iterations and generates with 30 iterations the following three displays:

Figure 3: Gradient display of neural discharges, summed over 30 iterations.

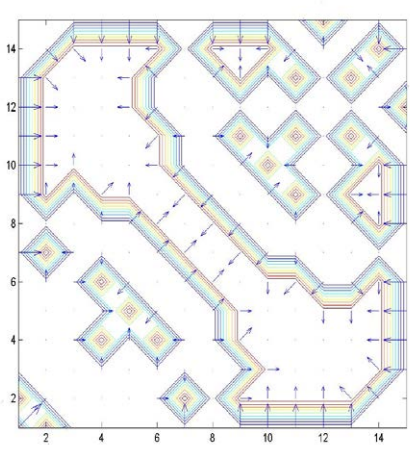


Figure 4: Contour plot of the summed neural activity of Figure 3: (the range is from 4 -brown- to 1 -dark blue- discharges, for each neuron.)

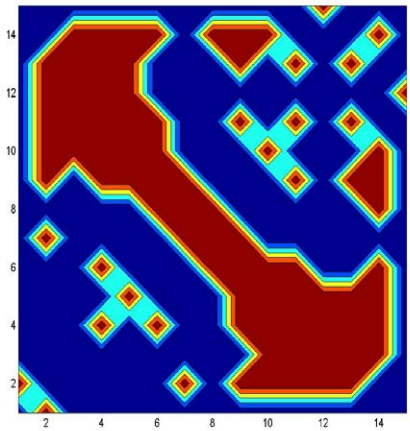
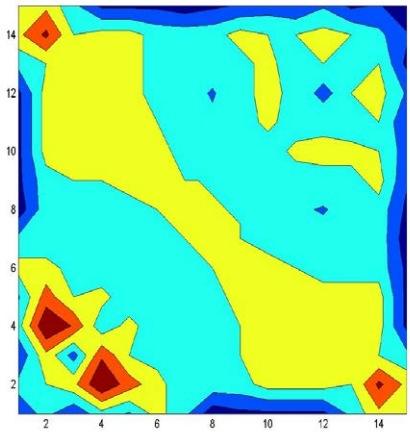


Figure 5: Contour plot of the I_T conductance values (reflecting the postulated reduction of Ca^{2+}) pertaining to the neural activity displays of Figures 3 and 4. (yellow marks peaks of the diffusion panorama, which after transformation to conductance values of I_T, lowers the threshold for excitation).



Except for minor fluctuations, activity and diffusion patterns remain essentially stable for 50 iterations, as if the activity in the neuron assembly had settled on an attractor or limit cycle. Note the general similarity in the pattern of relative increase in neuronal activity and the peaks in the diffusion pattern: the latter translate in the model to higher values of the I_T conductance, hence: reduced repolarization and increased neuron excitability.

In a second series of simulations, I examined the effect of diffusion associated with neural discharges in an array of 10x10 neurons, connected serially by excitatory electrical junctions to a ring structure (i.e. neuron (10,10) connects

back to neuron (1,1)). The neuron (1 1) in the array was stimulated repetitively, and the spread of excitation in the ring was determined in the presence and absence of diffusion. Figure 6 shows the activity in a 3D bar plot in the absence, and Figure 7in the presence of changing the I_T conductance in the diffusion model. The contrast between the displays of Figures 6 and 7 shows the effect of the diffusion induced changes in I_T conductance on the propagation of neural activity in the ring structure.

Figure 6:

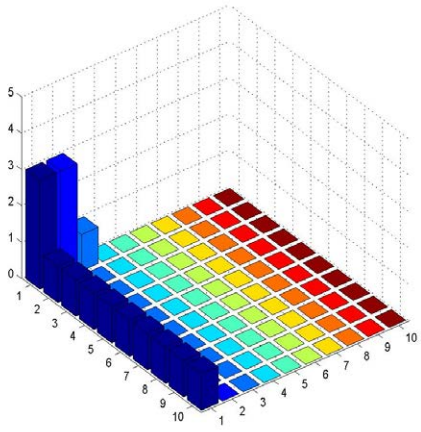


Figure 7:

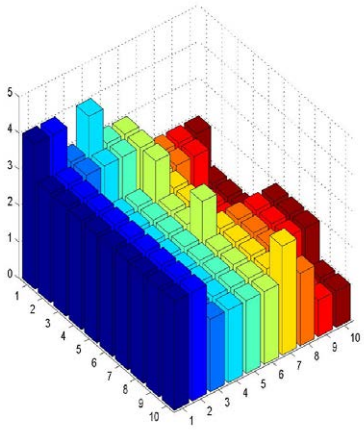
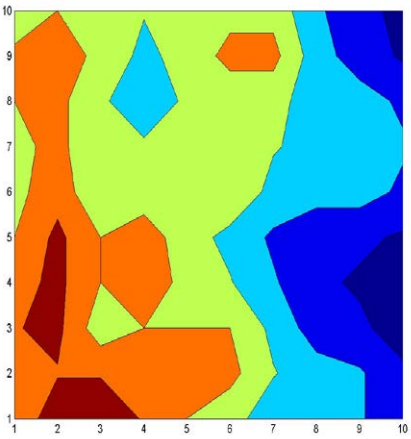


Figure 8 (below) shows the distribution of the computed Ca^{2+} concentration in the perineural space of the neuron ring whose activity is displayed in Fig. 7. The concentration gradient covers an 7-fold range, with sinks shown in shades of blue, and the source maximum in brown; other colours designate intermediate values.

Figure 8:



Discussion: Excitable Media.

The results illustrated in the foregoing support the initial conjecture that targeted changes in extracellular ion composition can by diffusion alter firing patterns across model neuron assemblies, in the absence of synaptic connections among the neurons, as well as with active electrical junctions. This observation warrants placing neurons and their extracellular environment in a broader conceptual framework. Neurons belong to the class of 'excitable media' in the sense that they undergo the typical sequence of transitions: active phases (excitation) preceded and followed by passive processes. In the case of a chemical system (exemplified by the Belousov - Zhabotinsky reaction, see: 62) , the characteristic cyclic transition rest - excitation - recovery the phase varies continuously with time, traversing regularly a full cycle. Astrocyte glia exemplifies this pattern in the form of the intracellular Ca - IP_3 cycle. In the case of the neuron, the system remains at rest until sufficiently perturbed at which time it runs through a full cycle. The phases of excitation and stationarity are in the former case mediated by diffusion, in the latter by passive electrononic current flow. An intrinsic property of excitable systems is that the alternation between the perturbed (excited) and the perturbing state (the extracellular medium) occur at different time scales: a fact which the models discussed in the foregoing do not take into account, but which undoubtedly are of significance. In a broader context, it

is also apparent from the work of Greengard (28) and others that neuromodulator related metabolic processes of neuronal tissue proceed at several time scales concurrently, ranging from msec to many 100 seconds.

The view of the neuron as excitable system considers the neuronal membrane as a whole as the excitable component, subject to the trigger action of spreading electrotonic current. The observations reported here suggest that more subtle and differentiated form neuron - medium interaction requires consideration: this time at the level of ionic channels and chemical medium. As carrier of diffusible substances, the extended medium of extracellular space functions as modulator of the excitability cycle of ion channels in the neuronal membrane. Yet, it is the neuron's activity which has set the propagating chemical wave in motion. Hence, neurons and their chemical matrix jointly impose a recursive dynamics on the system: the neuron's activity (as the excitable component) initiates the propagating disturbance across the extended medium; this, in turn, affects the excitability cycle of ion channels in very specific ways, depending on the nature and concentration of the chemical agents permeating the extracellular space in their vicinity.

In a metaphorical sense, the extracellular medium plays on ion channels like on keys of a piano, a metaphor that Pribram (47) introduced some time ago in another context. Two objectives are thereby achieved: one, a self-limiting control on the neuron from which the disturbance originates; the other, the coordinated effect of nearby neurons in an assembly which are in the range of effective diffusion. The staggering complexity that can result under such conditions from the concurrent activity of several neurons in an assembly is readily apparent: in fact, the simulations show how activity profiles can travel in time across assemblies, leading to a shifting panorama of activity levels across a group of neurons in mutual proximity.

The notion of excitable media is not a newcomer in theoretical Neuroscience: in the context of their fundamental mathematical characterization of the spread of excitation in the myocardium, N. Wiener and A. Rosenbluth (59) conjectured in 1946 that analogous principles may be operative in the nervous system, except for the excitability properties of neurons. Since that time, Winfree (63) has repeatedly reaffirmed his belief that myocardium and brain tissue share some aspects of the functional characteristics of excitable media.

The simulation data presented here, and the conceptual framework developed for their interpretation are, both, in need of substantial refinement and extension. However, granting that they are initial pointers of some merit, and elementary indicators of general principles, several implications follow: the activity patterns of neurons and their assemblies are interdependent with the extracellular milieu in which they are embedded, and to whose time varying composition they contribute. The complexity of this interdependence in the temporal dimension forecloses any time and context invariant relation between what the experimenter may consider stimulus input and its representation in neural activity. Hence, ideas of coding by (quasi)-digital neurons are called in question by the mutual interdependence of neurons and their humoral milieu. Instead, concepts of 'mass action' in the Nervous system gain a new perspective: this time augmented by including the chemical medium surrounding neurons as part of the dynamics of the system as a whole. Accordingly, a meaningful way to describe activity in a neuron assembly would be in terms of a state space in which it can move along an infinite number of trajectories, save for some possible constraints: the interesting question is what such constraint may be.

Footnote: Commentary on computational modeling and simulations:
Computational simulations generate consequences of algorithmically formalized theories, allowing either their falsification if not matching experimental reality, of guiding the experimentalist to seek validation of simulation pedictions. It is only in the sense of setting constraints that simulations generate new knowledge. In addition, it must of course be realized the simulations compute processes with real numbers on Turing Machines, while processes in nature may be (and generally are) of entirely different forms of 'computational' transformations: the nervous system does not 'compute' with numbers, but presumably with transformations of physical substrates (e.g. allosteric conformation of molecules). Moreover, the blurring of the distinction 'simulation' and modeling' must be guarded against: the latter being based on an abstract symbolic representation of a real system. Robert Rosen's long standing admonitions against conflating 'simulation' and 'modeling' are often overlooked. Simulations generate virtual objects whose reality potential is subject to verification. Consistence of terminology would require that objects of computational simulation be called 'Simulacra'. Genuine models, on the other hand, are symbolically encoded abstractions of real objects.

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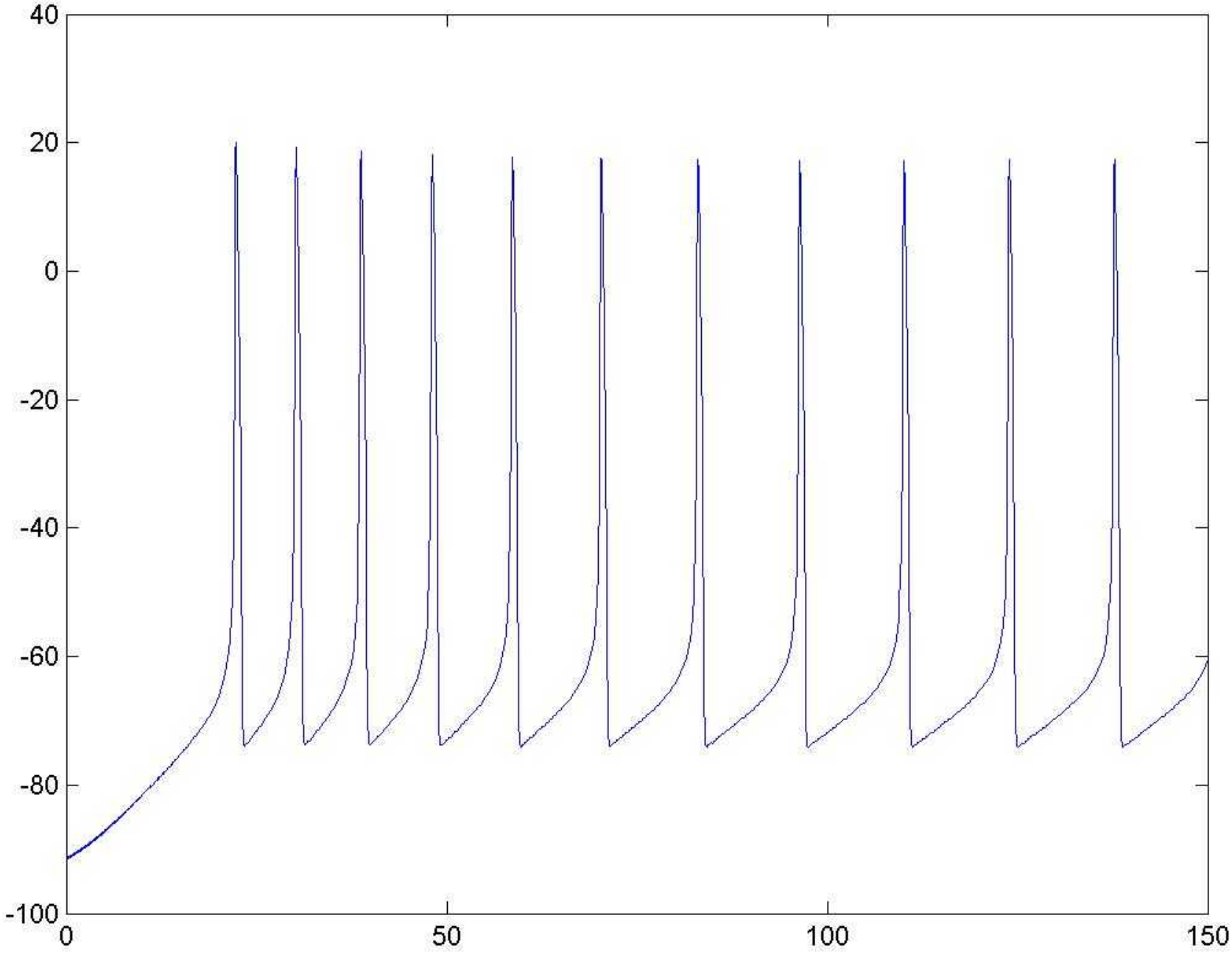
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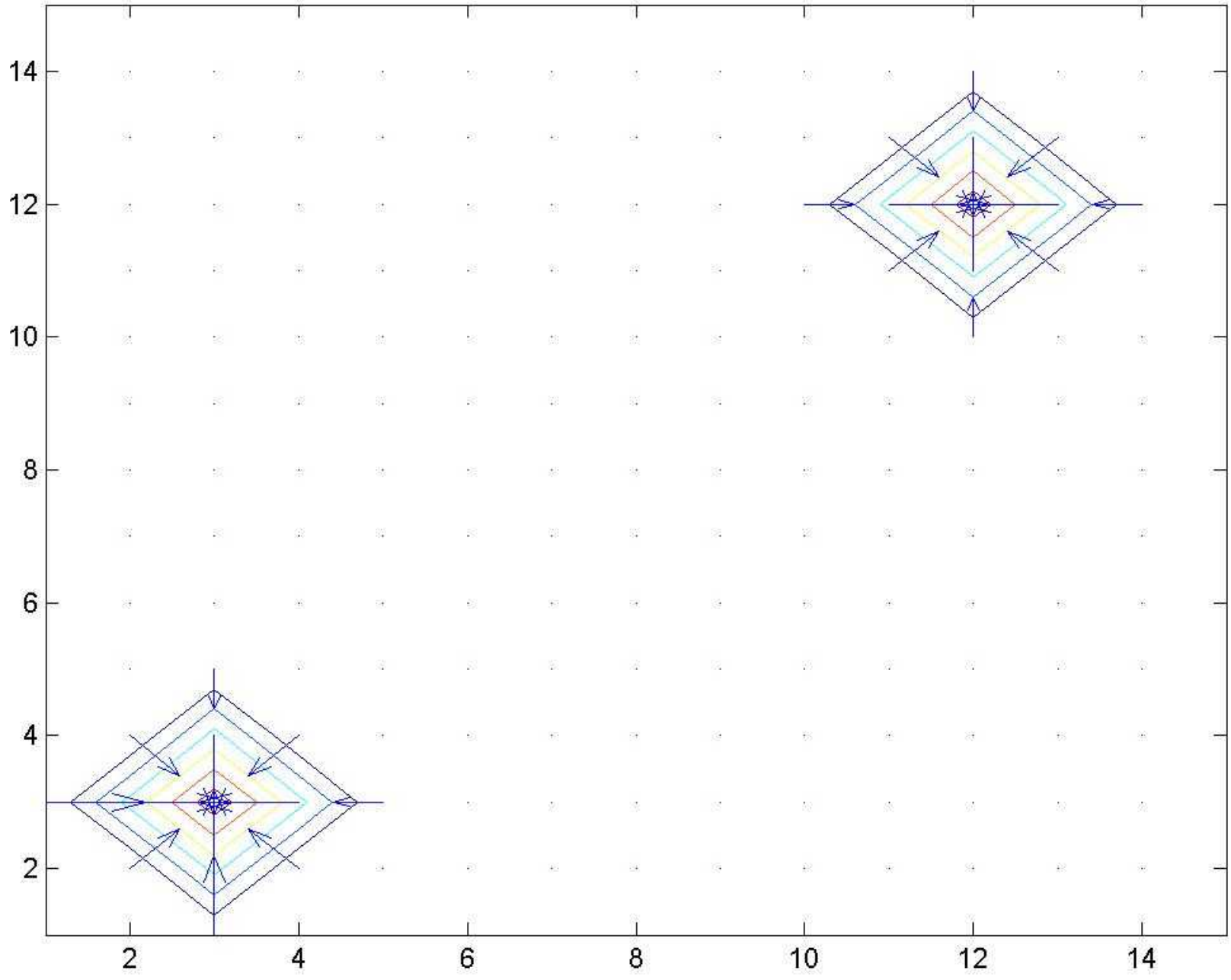
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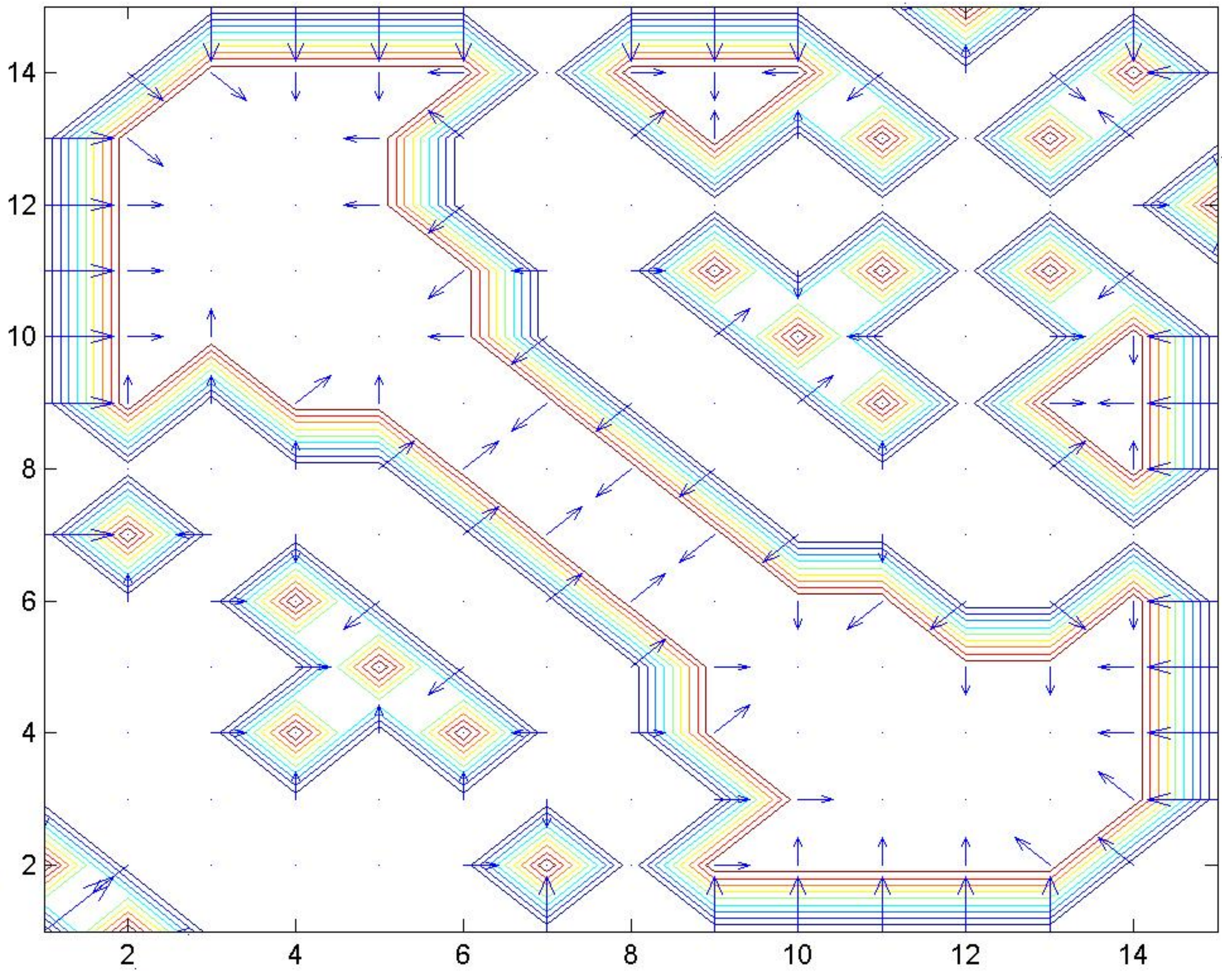
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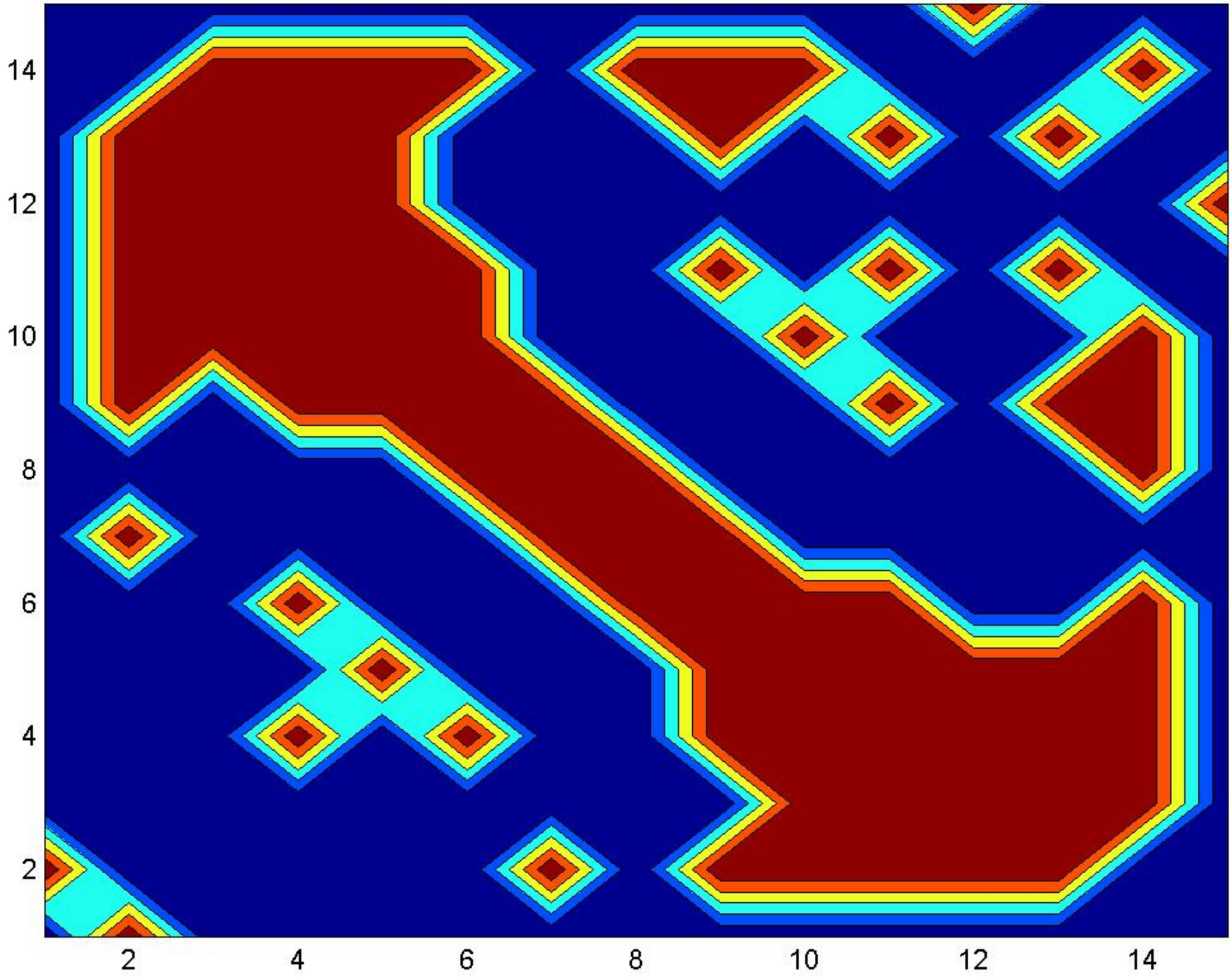
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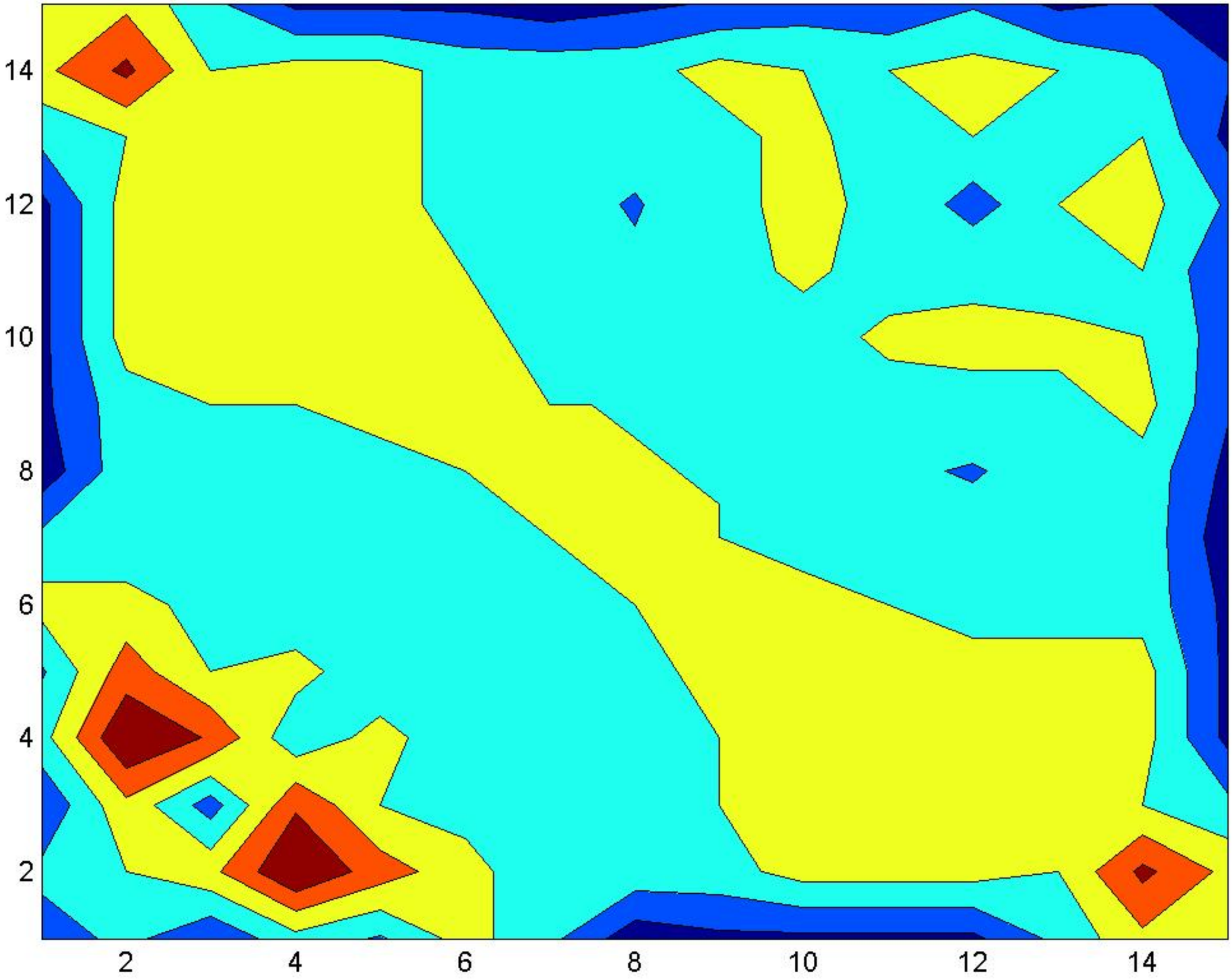
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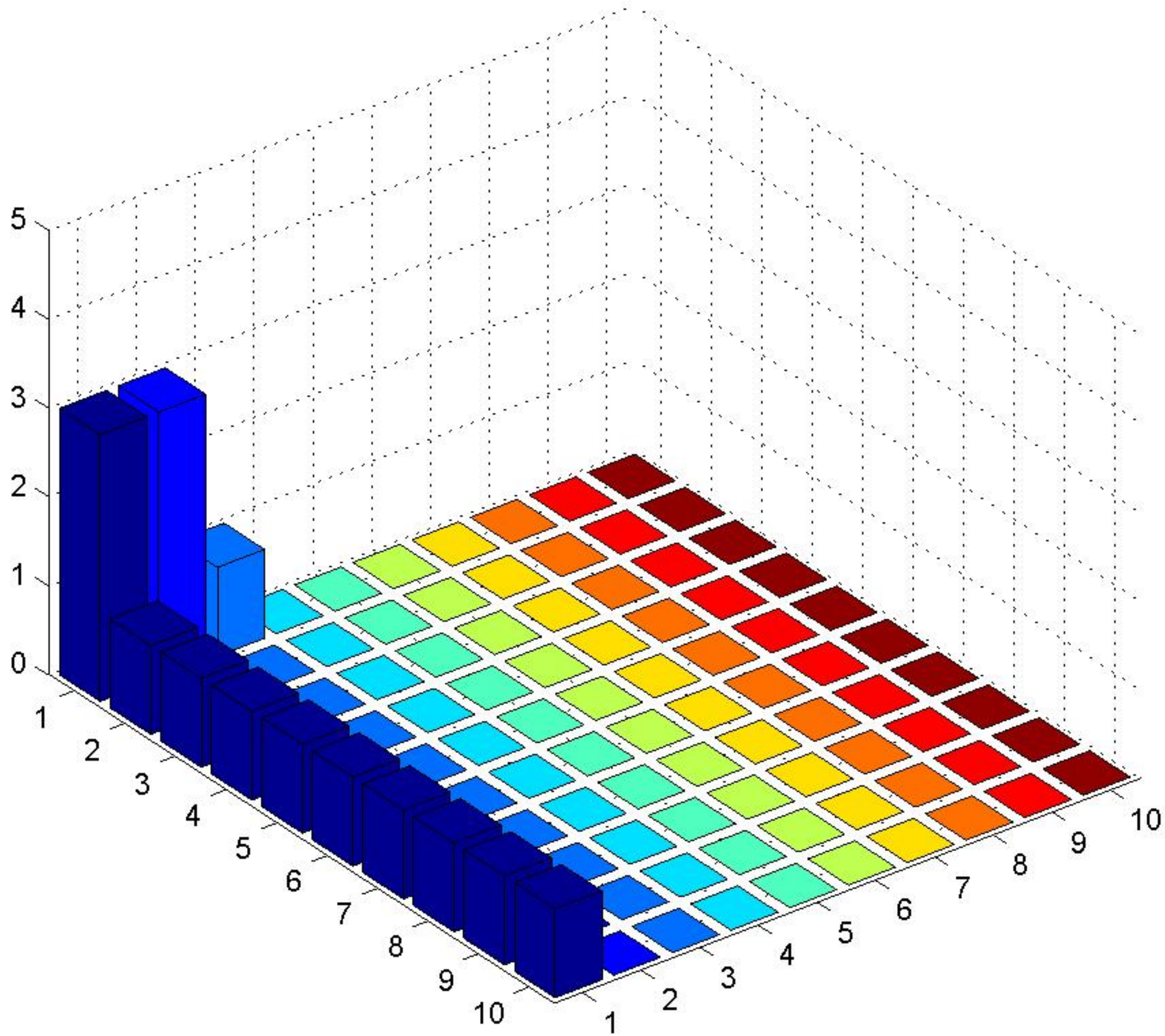
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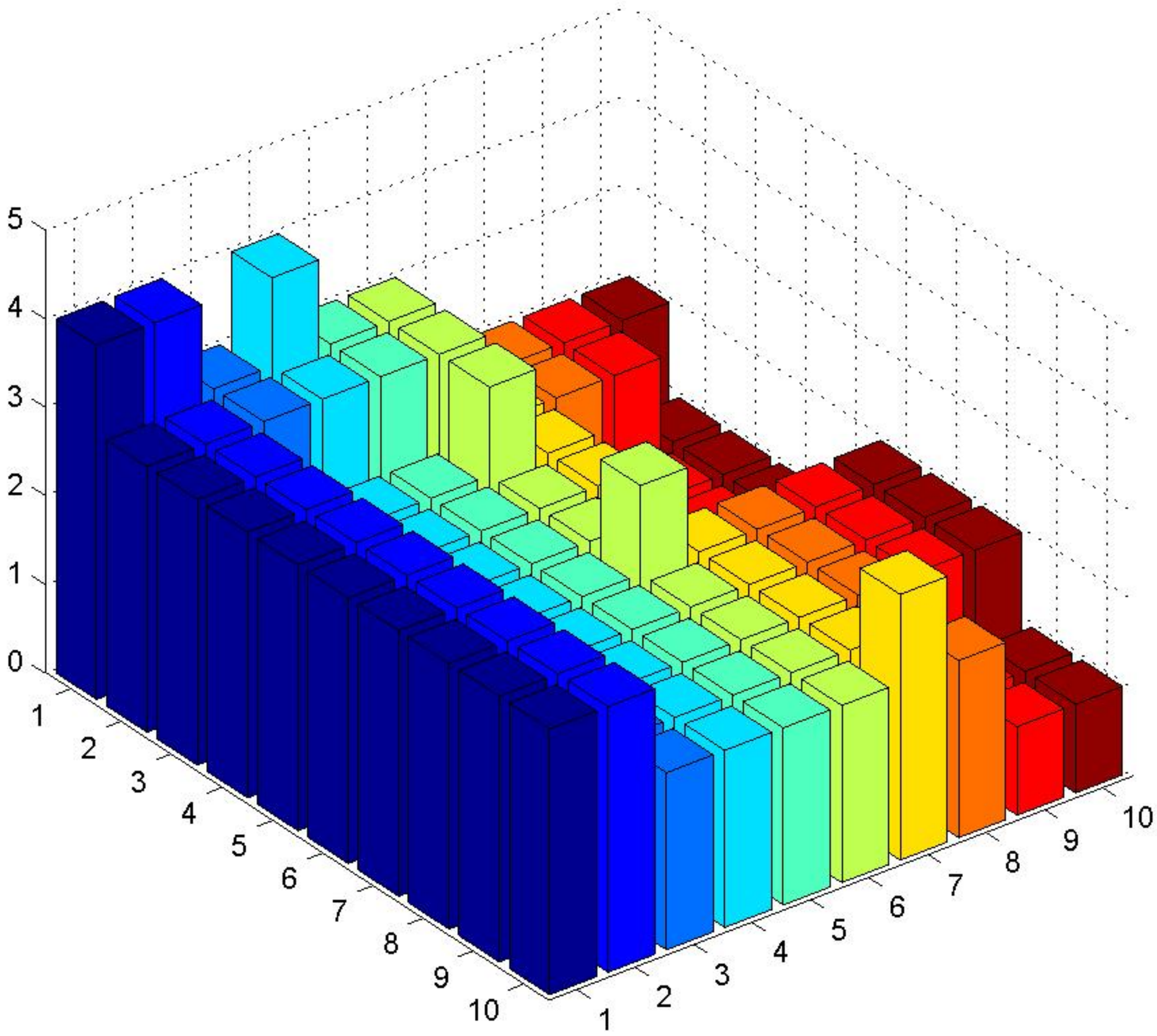
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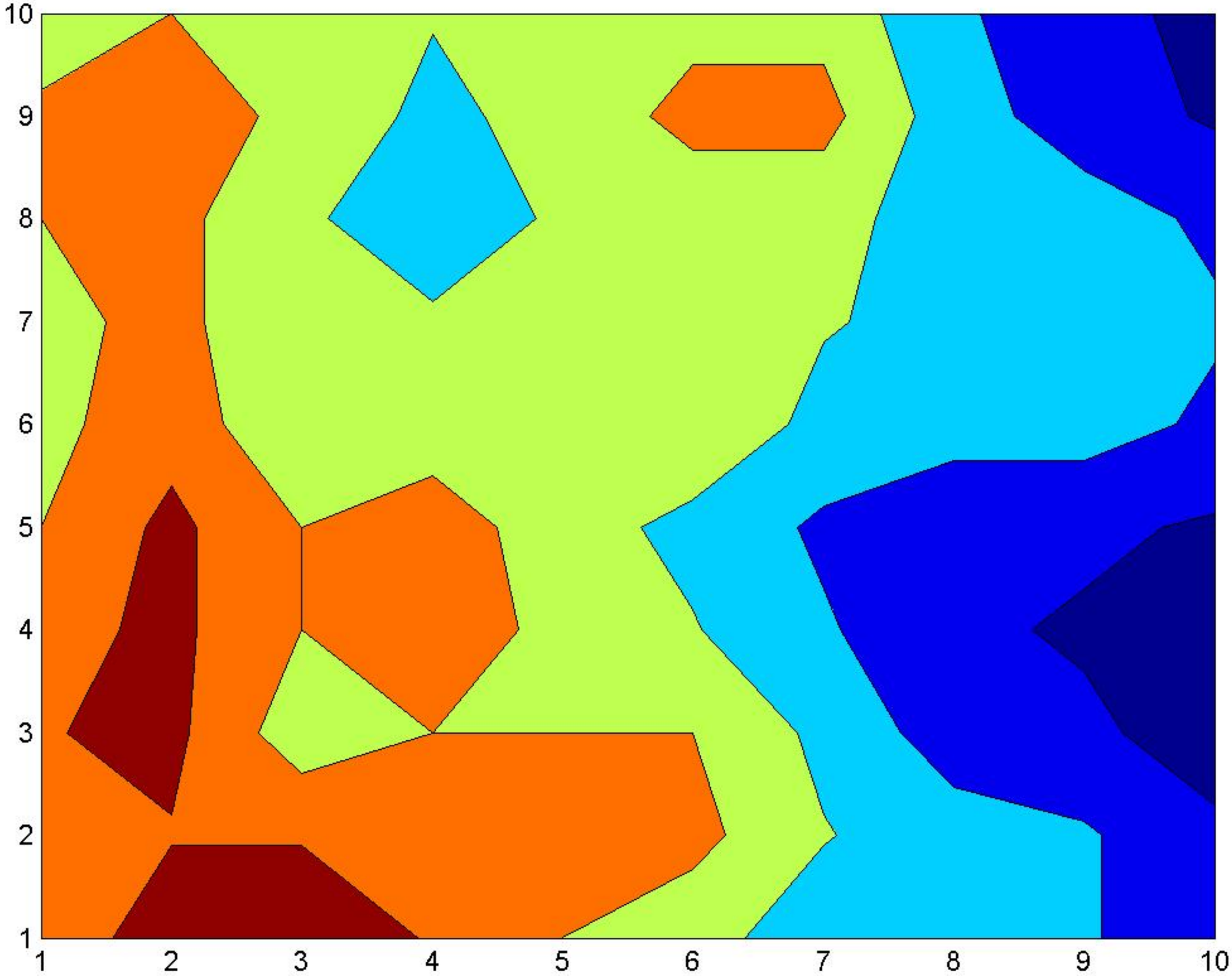
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